FENPICOXAMID

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Explanation

Fenpicoxamid is the International Organization for Standardization–approved common name for [2-[[(3*R*,7*R*,8*R*,9*S*)-7-benzyl-9-methyl-8-(2-methylpropanoyloxy)-2,6-dioxo-1,5-dioxonan-3-yl]-carbamoyl]-4-methoxypyridin-3-yl]oxymethyl 2-methylpropanoate, with the Chemical Abstracts Service (CAS) number 517875-34-2.

Fenpicoxamid is a foliar fungicide whose mode of action is by the inhibition of mitochondrial complex III to disrupt spore germination and germ tube elongation.

Fenpicoxamid has not previously been evaluated by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) and was reviewed by the present Meeting at the request of the Codex Committee on Pesticide Residues.

All critical studies contained statements of compliance with good laboratory practice (GLP) and were conducted in accordance with relevant national or international test guidelines, unless otherwise specified. No additional information from a literature search was identified that complemented the toxicological information submitted for the current assessment.

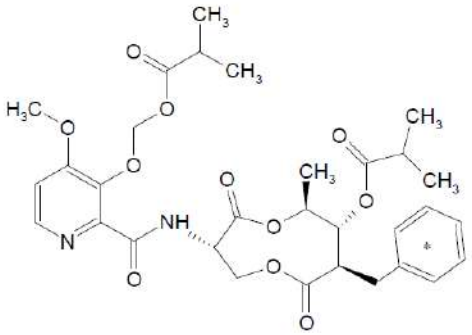
Evaluation for acceptable intake

1. Biochemical aspects

The absorption, distribution, metabolism and excretion of fenpicoxamid, as well as its toxicokinetics, have been investigated in F344 and Sprague Dawley rats, Crl:CD1 mice, New Zealand white rabbits and beagle dogs. Summaries of the relevant data are presented below.

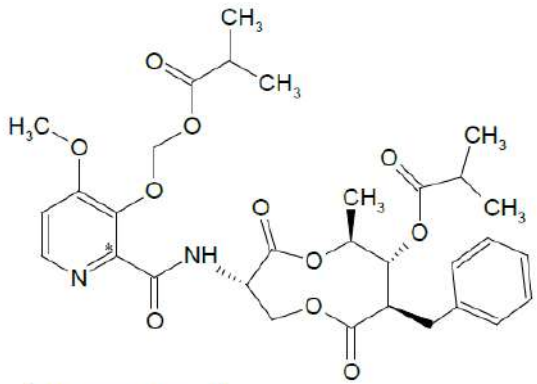
The absorption, distribution, metabolism and elimination (ADME) of fenpicoxamid were investigated using fenpicoxamid uniformly labelled (UL) on the phenyl ring (Fig. 1) or labelled at the pyridine-2 position (Fig. 2). The test item in the main studies was a mixture of ^{14}C-labelled and unlabelled fenpicoxamid, with a probe study performed with a mixture of ^{12}C-, ^{13}C- and ^{14}C-labelled fenpicoxamid. The study design is summarized in Table 1.

Fig. 1. [^{14}C-phenyl-UL]Fenpicoxamid



*XDE-777 phenyl-UL-^{14}C

Fig. 2. [^{14}C-2-pyridine]Fenpicoxamid



*XDE-777 pyridine-2-^{14}C

Table 1. Dosing groups for ADME experiments with ^{14}C-labelled fenpicoxamid

Test group	Dose (mg/kg bw) (route)	Number of animals of each sex	Remarks	Reference
Probe study – F344/NTac rats – time course rat blood (group 1)	65 (oral)	1 M	Single-dose mixture of [^{14}C-phenyl-UL]fenpicoxamid, [^{13}C-phenyl-UL]fenpicoxamid and unlabelled fenpicoxamid with target radioactivity of 3.0 MBq/kg bw in 0.5% methylcellulose Excreta, blood (plasma and RBCs), expired air, volatiles and time course plasma collected	Hansen et al. (2012)
Probe study – F344/NTac rats – rat excreta (group 2)	65 (oral)	1 M, 1 F	Single dose of [^{13}C-phenyl-UL]fenpicoxamid in 0.5% methylcellulose Excreta and blood collected	Hansen et al. (2012)
Probe study – F344/NTac rats – C_{max} rat blood (group 3)	65 (oral)	1 M	Single-dose mixture of [^{14}C-phenyl-UL]fenpicoxamid, [^{13}C-phenyl-UL]fenpicoxamid and unlabelled fenpicoxamid with target radioactivity of 3.0 MBq/kg bw in 0.5% methylcellulose Killed at C_{max}, and blood collected	Hansen et al. (2012)
Probe study – F344/NTac rats – C_{max} rat blood (group 4)	65 (oral)	1 F	Single dose of [^{13}C-phenyl-UL]fenpicoxamid in 0.5% methylcellulose Killed at C_{max}, and blood collected	Hansen et al. (2012)
Probe study – Crl:CD1 mice – time course mouse blood (group 5)	65 (oral)	2 M, 2 F	Single-dose mixture of [^{14}C-phenyl-UL]fenpicoxamid, [^{13}C-phenyl-UL]fenpicoxamid and fenpicoxamid with target radioactivity of 3.0 MBq/kg bw in 0.5% methylcellulose Excreta, blood, expired air and volatiles collected	Hansen et al. (2012)
Probe study – Crl:CD1 mice – C_{max} mouse blood (group 6)	65 (oral)	2 M, 2 F	Single-dose mixture of [^{14}C-phenyl-UL]fenpicoxamid, [^{13}C-phenyl-UL]fenpicoxamid and unlabelled fenpicoxamid with target radioactivity of 3.0 MBq/kg bw in 0.5% methylcellulose Killed at C_{max}, and blood collected	Hansen et al. (2012)
Probe study – F344/NTac rats – C_{max} rat blood (group 7)	65 (oral)	1 M, 1 F	Single-dose mixture of [^{14}C-phenyl-UL]fenpicoxamid and unlabelled fenpicoxamid with target radioactivity of 26	Hansen et al. (2012)

Test group	Dose (mg/kg bw) (route)	Number of animals of each sex	Remarks	Reference
			MBq/kg bw in 0.5% methylcellulose Killed 6 hours post-dosing, and excreta and blood collected; whole body autoradiography performed	
Probe study – F344/NTac rats – ½ C_{max} rat blood (group 8)	65 (oral)	1 M, 1 F	Single-dose mixture of [^{14}C-phenyl-UL]fenpicoxamid and unlabelled fenpicoxamid with target radioactivity of 26 MBq/kg bw in 0.5% methylcellulose Killed 12 hours post-dosing, and excreta and blood collected	Hansen et al. (2012)
Probe study – New Zealand white rabbits – time course rabbit blood (group 9)	30 (oral)	2 F	Single-dose mixture of [^{14}C-phenyl-UL]fenpicoxamid and unlabelled fenpicoxamid in 0.5% methylcellulose Excreta and blood collected Time course blood collected	Hansen et al. (2012)
Probe study – New Zealand white rabbits – time course rabbit blood (group 10)	10 (iv)	2 F	Single-dose mixture of [^{14}C-phenyl-UL]fenpicoxamid and unlabelled fenpicoxamid in 10% intralipid emulsion Excreta and blood collected Time course blood collected	Hansen et al. (2012)
Probe study – F344/NTac rats – time course rat blood (group 11)	10 (oral)	2 M	Single-dose mixture of [^{14}C-phenyl-UL]fenpicoxamid and unlabelled fenpicoxamid in 0.5% methylcellulose Time course plasma, excreta and blood collected	Hansen et al. (2012)
Probe study – F344/NTac rats – time course rat blood (group 12)	1 (iv)	2 M	Single-dose mixture of [^{14}C-phenyl-UL]fenpicoxamid and unlabelled fenpicoxamid in 10% intralipid emulsion Time course plasma, excreta and blood collected	Hansen et al. (2012)
Probe study – beagle dogs – time course dog blood and excreta	30 (oral)	1 M, 1 F	Single-dose mixture of [^{14}C-pyridine]fenpicoxamid and unlabelled fenpicoxamid in 0.5% (w/v) METHOCEL Time course blood, urine and faeces collected	Thomas (2012)
Tissue distribution – F344/DuCrl rats – C_{max}	10 (oral)	4 M, 4 F	Single-dose mixture of [^{14}C-phenyl-UL]fenpicoxamid and unlabelled fenpicoxamid Killed at C_{max} (2 hours post-dosing)	Hansen, Clark & Staley (2012)

Test group	Dose (mg/kg bw) (route)	Number of animals of each sex	Remarks	Reference
Tissue distribution – F344/DuCrl rats – ½ C_{max}	10 (oral)	4 M, 4 F	Single-dose mixture of [^{14}C-phenyl-UL]fenpicoxamid and unlabelled fenpicoxamid Killed at ½ C_{max} (6 hours post-dosing)	Hansen, Clark & Staley (2012)
Tissue distribution – F344/DuCrl rats – C_{max}	300 (oral)	4 M, 4 F	Single-dose mixture of [^{14}C-phenyl-UL]fenpicoxamid and unlabelled fenpicoxamid Killed at C_{max} (2 hours post-dosing)	Hansen, Clark & Staley (2012)
Tissue distribution – F344/DuCrl rats – ½ C_{max}	300 (oral)	4 M, 4 F	Single-dose mixture of [^{14}C-phenyl-UL]fenpicoxamid and unlabelled fenpicoxamid Killed at ½ C_{max} (12 hours post-dosing)	Hansen, Clark & Staley (2012)
Absorption and excretion – Sprague Dawley rats – bile duct cannulation – time course rat bile and excreta	10 (oral)	4 M, 4 F	Single-dose mixture of [^{14}C-2-pyridine]fenpicoxamid and unlabelled fenpicoxamid in 0.5% (w/v) METHOCEL Time course bile, urine and faeces collected Killed at 72 hours post-dosing	Press & Reynolds (2013)
Absorption and excretion – Sprague Dawley rats – bile duct cannulation – time course rat bile and excreta	300 (oral)	4 M, 4 F	Single-dose mixture of [^{14}C-2-pyridine]fenpicoxamid and unlabelled fenpicoxamid in 0.5% (w/v) METHOCEL Time course bile, urine and faeces collected	Press & Reynolds (2013)
Pharmacokinetics and metabolism – F344/DuCrl rats	10 (oral)	4 M, 4 F	Single-dose mixture of [^{14}C-phenyl-UL]fenpicoxamid and unlabelled fenpicoxamid	Hansen et al. (2013)
Pharmacokinetics and metabolism – F344/DuCrl rats	300 (oral)	4 M, 4 F	Single-dose mixture of [^{14}C-phenyl-UL]fenpicoxamid and unlabelled fenpicoxamid	Hansen et al. (2013)
Pharmacokinetics and metabolism – F344/DuCrl rats	10 (oral)	4 M, 4 F	Single-dose mixture of [^{14}C-2-pyridine]fenpicoxamid and unlabelled fenpicoxamid	Hansen et al. (2013)
Pharmacokinetics and metabolism – F344/DuCrl rats	10 (oral)	4 M, 4 F	Repeated oral doses of unlabelled fenpicoxamid (14 doses) and single-dose mixture of [^{14}C-phenyl-UL]fenpicoxamid and unlabelled fenpicoxamid	Hansen et al. (2013)
In vitro comparative metabolism study – mouse liver microsome	0.065 µmol/L		Single exposure to mixture of [^{14}C-2-pyridine]fenpicoxamid and unlabelled fenpicoxamid	Zhang et al. (2014)
In vitro comparative metabolism study – rat liver microsome	0.065 µmol/L		Single exposure to mixture of [^{14}C-2-pyridine]fenpicoxamid and unlabelled fenpicoxamid	Zhang et al. (2014)

Test group	Dose (mg/kg bw) (route)	Number of animals of each sex	Remarks	Reference
In vitro comparative metabolism study – human liver microsome	0.065 µmol/L		Single exposure to mixture of [^{14}C-2-pyridine]fenpicoxamid and unlabelled fenpicoxamid	Zhang et al. (2014)

bw: body weight; C_{max}: maximum concentration; F: female; iv: intravenous; M: male; RBCs: red blood cells; UL: uniformly labelled; w/v: weight per volume

1.1 Absorption, distribution and excretion

(a) Oral and intravenous routes

Preliminary ADME assays were performed on rats, mice and rabbits. Orally administered fenpicoxamid was rapidly absorbed in the rat and rabbit. Time to reach maximum concentration values (T_{max}) were 6 and 2 hours, respectively, and area under the plasma concentration–time curve from time 0 to infinity values ($AUC_{0-\infty}$) were 38.4 and 24.1 µg·h/g, respectively, in rats and rabbits given an oral dose of 65 mg/kg body weight (bw). Of the animals given 65 mg/kg bw orally, male rats and male mice excreted 12% of the administered dose in the urine, whereas female mice excreted 25% and female rabbits excreted 42% of the administered dose in the urine. In rats given 10 mg/kg bw, 15% was excreted in the urine of rats dosed orally, whereas 26% was excreted in the urine of rats dosed intravenously. Rabbits given 10 mg/kg bw intravenously died immediately upon dosing (Hansen et al., 2012).

A preliminary ADME assay was performed in beagle dogs. The T_{max} was 2 hours post-dosing, with 1% of the administered dose excreted in the urine and 90% excreted in the faeces. Biliary excretion was not investigated, nor was the recovered radioactivity characterized to determine whether the parent was metabolized. Excretion was rapid, occurring mostly in 24 hours (Thomas, 2012).

Tissue distribution was investigated in F344/DuCrl rats (four of each sex per dose) following administration of a single radiolabelled dose of 0, 10 or 300 mg [^{14}C-phenyl-UL]fenpicoxamid/kg bw. Tissues were collected at the maximum concentration (C_{max}) and ½ C_{max}. Tissue distribution was extensive, but low at the C_{max}, with most tissues accounting for less than 0.01% of the administered dose. The majority of radioactivity (92–99%) was recovered in the gastrointestinal tract, regardless of dose or sex, followed by the urinary bladder, liver and kidneys (Table 2).

Table 2. Distribution of radioactivity in rat tissues/organs at C_{max} and ½ C_{max} after administration of ^{14}C-labelled fenpicoxamid[a]

Tissue/ organ	Concentration of radioactivity in tissues/organs							
	10 mg/kg bw				300 mg/kg bw			
	C_{max}		½ C_{max}		C_{max}		½ C_{max}	
	Males	Females	Males	Females	Males	Females	Males	Females
Bladder								
µg eq/g tissue	2.97 ± 0.67	5.08 ± 4.82	3.22 ± 1.60	2.19 ± 1.41	17.70 ± 7.77	2.21 ± 1.17	5.33 ± 1.28	9.45 ± 6.30
% AD	0.01	0.02	0.01	0.01	<0.01	<0.01	<0.01	<0.01
Blood								
µg eq/g tissue	0.62 ± 0.07	0.76 ± 0.10	0.15 ± 0.10	0.58 ± 0.11	1.98 ± 0.30	2.07 ± 0.32	0.87 ± 0.23	1.18 ± 0.21

Tissue/ organ	Concentration of radioactivity in tissues/organs							
	10 mg/kg bw				300 mg/kg bw			
	C_{max}		½ C_{max}		C_{max}		½ C_{max}	
	Males	Females	Males	Females	Males	Females	Males	Females
% AD	0.19	0.22	0.12	0.17	0.02	0.02	0.01	0.01
Carcass								
µg eq/g tissue	0.17 ± 0.03	0.20 ± 0.05	0.14 ± 0.02	0.15 ± 0.06	0.51 ± 0.13	0.86 ± 0.39	0.32 ± 0.13	0.37 ± 0.07
% AD	0.89	1.05	0.72	0.81	0.10	0.18	0.07	0.07
GI tract								
µg eq/g tissue	120.56 ± 7.15	106.93 ± 5.73	98.79 ± 6.31	79.63 ± 6.31	3 809 ± 201	3 098 ± 232	1 274 ± 257	1 414 ± 346
% AD	92.23	92.87	86.89	87.42	98.68	97.82	52.36	58.96
Kidney								
µg eq/g tissue	1.14 ± 0.18	1.05 ± 0.12	0.91 ± 0.13	0.88 ± 0.15	3.93 ± 0.67	3.34 ± 0.38	3.38 ± 1.86	1.77 ± 0.30
% AD	0.08	0.07	0.06	0.06	0.01	0.01	0.01	<0.01
Liver								
µg eq/g tissue	2.60 ± 0.42	2.32 ± 0.20	1.22 ± 0.46	1.32 ± 0.21	8.18 ± 1.56	6.64 ± 0.73	3.82 ± 1.02	2.83 ± 0.27
% AD	0.72	0.61	0.35	0.40	0.08	0.07	0.05	0.03
Lungs								
µg eq/g tissue	0.56 ± 0.05	0.67 ± 0.10	0.44 ± 0.10	0.52 ± 0.07	1.76 ± 0.73	2.10 ± 0.75	1.06 ± 0.34	1.05 ± 0.19
% AD	0.03	0.04	0.02	0.03	<0.01	<0.01	<0.01	<0.01
Skin								
µg eq/g tissue	0.23 ± 0.04	0.25 ± 0.07	0.15 ± 0.02	0.22 ± 0.04	0.66 ± 0.10	0.62 ± 0.12	0.38 ± 0.12	0.34 ± 0.04
% AD	0.43	0.44	0.28	0.37	0.05	0.04	0.03	0.02
Testes								
µg eq/g tissue	0.27 ± 0.05	NA	0.21 ± 0.04	NA	0.69 ± 0.13	NA	0.83 ± 0.19	NA
% AD	0.03	NA	0.02	NA	<0.01	NA	<0.01	NA
Final cage wash (% AD)	1.73	1.30	3.73	5.88	0.17	0.25	42.19	34.63
Total recovered radioactivity (% AD)	96.37 ± 1.42	96.69 ± 0.45	92.23 ± 1.89	95.19 ± 2.60	99.13 ± 1.29	98.41 ± 0.36	94.72 ± 1.80	93.74 ± 2.99

AD: administered dose; bw: body weight; eq: equivalents; C_{max}: maximum concentration; GI: gastrointestinal; NA: not applicable

[a] Tissues/organs lacking quantifiable radioactivity or radioactivity counts greater than 0.01% of the administered dose in at least one dose group were excluded from the table.

Source: Data obtained from pages 30–41 in Hansen, Clark & Staley (2012)

At the high dose, tissue/organ concentrations were 2- to 3-fold higher than at the low dose, and tissue/organ concentrations did not scale proportionately to the administered dose. However, there were no major changes to the pattern of tissue/organ distribution between doses or between sexes. Rapid elimination occurred in all tissues (Hansen, Clark & Staley, 2012).

In an excretion study in bile duct–cannulated Sprague Dawley rats, animals were given [^{14}C-2-pyridine]fenpicoxamid at a single oral dose of 10 or 300 mg/kg bw. Concentrations in the blood, cellular fraction and plasma confirmed that absorption was rapid, peaking at 2 hours, but concentrations did not scale proportionately between the low and high doses (Table 3). At the high dose, blood plasma concentrations were higher in males than in females, and plasma concentrations were higher than concentrations in the cellular fraction. At the low dose, sex differences were less marked, although plasma concentrations were higher than concentrations in the cellular fraction.

Table 3. Concentrations of radioactivity in blood, cellular fraction and plasma of bile duct–cannulated rats following a single oral dose of [^{14}C-2-pyridine]fenpicoxamid at 10 or 300 mg/kg bw

	Mean (± SD) concentrations of radioactivity (ng fenpicoxamid eq/g)					
	10 mg/kg bw			**300 mg/kg bw**		
Time (h)	**Blood**	**Cellular fraction**	**Plasma**	**Blood**	**Cellular fraction**	**Plasma**
Males						
2	224 ± 51.3	125 ± 24.1	418 ± 123	1 230 ± 630	620 ± 296	2 230 ± 1 150
9	103 ± 36.5	55.2 ± 8.1	190 ± 61	1 170 ± 878	610 ± 319	2 110 ± 1 690
Females						
2	237 ± 50.5	118 ± 18.7	403 ± 89.7	809 ± 93.3	436 ± 58.8	1 230 ± 201
9	165 ± 57.9	90.1 ± 44.1	261 ± 103	680 ± 135	353 ± 81.4	1 080 ± 255

bw: body weight; eq: equivalents; SD: standard deviation
Source: Data obtained from pages 26–27 in Press & Reynolds (2013)

Recovery of administered radioactivity in the excreta and carcass was 89–99%. Biliary excretion was higher than excretion in the urine, indicating that absorption was higher than estimated in the other studies; however, the highest levels of recovered radioactivity were in the faeces (Table 4). Regardless of dose, elimination was rapid, peaking at 8 hours in the urine and in the first 24 hours in the faeces and bile.

Table 4. Recovery of radioactivity in excreta and carcass of bile duct–cannulated rats after administration of a single dose of [^{14}C-2-pyridine]fenpicoxamid

	% of administered dose recovered (± SD)			
	10 mg/kg bw		**300 mg/kg bw**	
Excreta with collection intervals (h)	**Males**	**Females**	**Males**	**Females**
Urine				
0–4	0.10 ± 0.18	0.13 ± 0.27	0.02 ± 0.03	0.01 ± 0.02
4–8	1.24 ± 0.58	1.09 ± 0.26	0.19 ± 0.05	0.09 ± 0.05
8–12	0.31 ± 0.10	0.18 ± 0.19	0.06 ± 0.05	0.04 ± 0.04
12–24	0.34 ± 0.16	0.99 ± 0.26	0.45 ± 0.63	0.11 ± 0.03
24–48	0.10 ± 0.03	0.31 ± 0.13	0.23 ± 0.39	0.05 ± 0.02

Excreta with collection intervals (h)	% of administered dose recovered (± SD)			
	10 mg/kg bw		300 mg/kg bw	
	Males	Females	Males	Females
48–72	0.02 ± 0.01	0.03 ± 0.01	0.02 ± 0.02	0.01 ± 0.01
Total	2.10 ± 0.61	2.75 ± 0.35	0.96 ± 1.10	0.31 ± 0.06
Faeces				
0–12	35.7 ± 11.7	7.97 ± 14.2	45.0 ± 15.7	8.46 ± 14.6
12–24	32.47 ± 9.98	58.9 ± 17.1	35.3 ± 5.21	76.8 ± 20.0
24–48	3.10 ± 0.69	12.4 ± 7.9	5.60 ± 3.40	11.1 ± 5.02
48–72	0.16 ± 0.15	1.81 ± 2.65	0.22 ± 0.15	0.21 ± 0.22
Total	71.7 ± 6.44	81.0 ± 3.17	86.1 ± 13.3	96.5 ± 3.01
Cage rinse				
0–4	0.67 ± 0.80	0.77 ± 0.56	0.23 ± 0.16	0.05 ± 0.03
4–8	0.57 ± 0.25	0.65 ± 0.28	0.10 ± 0.09	0.09 ± 0.02
8–12	0.26 ± 0.12	0.31 ± 0.19	0.11 ± 0.09	0.04 ± 0.02
12–24	0.13 ± 0.06	0.36 ± 0.08	0.07 ± 0.05	0.04 ± 0.01
24–48	0.04 ± 0.02	0.08 ± 0.03	0.07 ± 0.10	0.02 ± 0.01
Total	1.66 ± 0.47	2.17 ± 0.32	0.57 ± 0.39	0.23 ± 0.04
Final cage wash	0.04 ± 0.03	0.06 ± 0.02	0.07 ± 0.10	0.02 ± 0.01
Final cage wipe	0.50 ± 0.37	0.84 ± 0.30	0.21 ± 0.18	0.07 ± 0.07
Bile				
0–4	4.75 ± 1.45	3.12 ± 1.40	0.09 ± 0.18	0.39 ± 0.03
4–8	5.18 ± 0.70	3.49 ± 0.79	0.31 ± 0.13	0.45 ± 0.03
8–12	2.20 ± 0.57	2.50 ± 0.46	0.27 ± 0.18	0.36 ± 0.04
12–24	1.18 ± 0.40	2.51 ± 0.39	0.28 ± 0.22	0.48 ± 0.13
24–48	0.10 ± 0.06	0.33 ± 0.25	0.10 ± 0.03	0.17 ± 0.07
48–72	0.003 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.04
Total	13.4 ± 0.89	12.0 ± 2.31	1.05 ± 0.65	1.86 ± 0.13
Bile cannula	0.003 ± 0.002	0 ± 0	0.002 ± 0.003	0 ± 0
Jacket rinse[a]	0 ± 0	0 ± 0	0.001 ± 0.001	0 ± 0
Residual carcass	0.035 ± 0.004	0.04 ± 0.02	0.03 ± 0.12	0.009 ± 0.017
Total recovery	89.4 ± 7.17	98.9 ± 1.14	89.0 ± 11.8	99.0 ± 2.85

bw: body weight; SD: standard deviation

[a] Jacket-and-tether system used to hold bile cannula in place was rinsed to collect residual radioactivity.

Source: Data obtained from pages 28–31 in Press & Reynolds (2013)

Pharmacokinetics was examined with the phenyl and pyridine labels in single-dose and repeated-dose oral studies with rats (Table 5). Absorption was rapid (T_{max} 2–4 hours), regardless of dose, dose regimen or label, but low, at 5–20% of the administered dose. The pyridine label had a generally lower AUC value than the phenyl label, with higher AUC values in females than in males. The exception was in the high-dose group, where there were no sex differences in AUC.

Table 5. Plasma and blood pharmacokinetic parameters for rats given a single dose of ^{14}C-labelled fenpicoxamid

	Phenyl label				Pyridine label	
	10 mg/kg bw		300 mg/kg bw		10 mg/kg bw	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
Plasma						
T_{max} (h)	2 ± 0	2.25 ± 0.5	4.67 ± 2.31	2 ± 0	2 ± 0	1.75 ± 0.5
C_{max} (µg/g)	1.86 ± 0.64	2.13 ± 0.39	3.54 ± 0.67	4.50 ± 0.48	1.29 ± 0.16	1.50 ± 0.23
Absorption $t_{½}$ (h)	0.58 ± 0.21	0.59 ± 0.43	0.56 ± 0.10	0.58 ± 0.09	0.59 ± 0.17	0.45 ± 0.17
Elimination $t_{½\alpha}$ (h)	4.37 ± 1.03	5.92 ± 1.80	12.11 ± 1.47	9.72 ± 1.35	4.97 ± 0.88	6.37 ± 1.15
Elimination $t_{½\beta}$ (h)	35.38 ± 25.48	23.73 ± 5.75	NA	NA	53.39 ± 34.53	61.75 ± 14.48
$AUC_{0–168\ h}$ (µg·h/g)	18.95 ± 2.23	23.73 ± 5.75	NA	NA	13.17 ± 0.97	18.89 ± 3.45
$AUC_{0–48\ h}$ (µg·h/g)	15.52 ± 3.07	22.25 ± 5.31	74.41 ± 13.24	73.32 ± 12.43	NA	NA
Blood cells[a]						
T_{max} (h)	1.75 ± 0.5	1.75 ± 0.96	–	–	2 ± 0	1.5 ± 0.58
C_{max} (µg/g)	0.19 ± 0.03	0.29 ± 0.11	–	–	0.12 ± 0.03	0.18 ± 0.07
Absorption $t_{½}$ (h)	0.27 ± 0.08	0.28 ± 0.15	–	–	0.45 ± 0.19	0.43 ± 0.12
Elimination $t_{½\alpha}$ (h)	57.64 ± 5.18	50.80 ± 2.44	–	–	0.66 ± 0.44	1.26 ± 1.24
Elimination $t_{½\beta}$ (h)	NA	NA	–	–	9.39 ± 2.59	11.21 ± 1.38
$AUC_{0–168\ h}$ (µg·h/g)	10.40 ± 1.99	11.25 ± 1.53	–	–	NA	NA
$AUC_{0–24\ h}$ (µg·h/g)	2.23 ± 0.88	3.53 ± 0.44	–	–	0.84 ± 0.27	1.29 ± 0.39

AUC: area under the concentration–time curve; bw: body weight; C_{max}: maximum concentration; NA: parameter not calculated for this group; $t_{½}$: half-life; T_{max}: time to reach maximum concentration

[a] Not enough data points to model red blood cell pharmacokinetic parameters for 300 mg/kg bw.

Source: Data obtained from Tables 7 and 8, pages 65–66, in Hansen et al. (2013)

Comparison of tissue distribution showed low retention in the tissues and no major differences between labels (Table 6). There was no evidence of bioaccumulation.

Excretion was rapid (58–90% of the administered dose within 24 hours) and was predominantly via the faeces. Almost all radioactivity had been excreted by 48 hours. Comparatively more radioactivity was excreted via the urine at low doses with the phenyl label than at high doses, and generally less was excreted in the urine with the pyridine label (Table 7).

(b) Dermal route

No studies were submitted.

Table 6. Distribution of radioactivity in rat tissues/organs 168 hours after administration of ^{14}C-labelled fenpicoxamid[a]

	Concentration of radioactivity in tissues/organs							
	Phenyl label						**Pyridine label**	
	1 × 10 mg/kg bw		**1 × 300 mg/kg bw**		**15 × 10 mg/kg bw[b]**		**1 × 10 mg/kg bw**	
Tissue/organ	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
Blood								
µg eq/g tissue	0.013 ± 0.002	0.006 ± 0.007	NQ	NQ	0.012 ± 0.003	0.017 ± 0.004	NQ	0.004 ± 0.005
% AD	<0.01	<0.01	NQ	NQ	<0.01	0.01	NQ	<0.01
Heart								
µg eq/g tissue	0.003 ± 0.001	0.003 ± 0.001	NQ	NQ	0.002 ± 0.001	0.003 ± 0.001	0.001 ± 0.0	0.002 ± 0.0
% AD	<0.01	<0.01	NQ	NQ	<0.01	<0.01	<0.01	<0.01
Kidneys								
µg eq/g tissue	0.010 ± 0.002	0.015 ± 0.005	NQ	NQ	0.009 ± 0.002	0.014 ± 0.003	NQ	0.008 ± 0.001
% AD	<0.01	<0.01	NQ	NQ	<0.01	<0.01	NQ	<0.01
Liver								
µg eq/g tissue	0.013 ± 0.004	0.006 ± 0.006	NQ	NQ	0.013 ± 0.003	0.006 ± 0.005	NQ	NQ
% AD	0.01	<0.01	NQ	NQ	0.01	<0.01	NQ	NQ
Lungs								
µg eq/g tissue	0.005 ± 0.001	0.005 ± .001	0.054 ± 0.012	0.050 ± 0.007	0.005 ± 0.001	0.006 ± 0.001	0.002 ± 0.0	0.003 ± 0.0
% AD	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Pancreas								
µg eq/g tissue	0.002 ± 0.0	0.003 ± 0.001	0.035 ± 0.008	NQ	0.003 ± 0.003	NQ	NQ	NQ
% AD	<0.01	<0.01	<0.01	NQ	<0.01	NQ	NQ	NQ
Plasma								
µg eq/g tissue	–	–	–	–	0.005 ± 0.001	0.006 ± 0.002	–	–
% AD					<0.01	<0.01		
RBCs								
µg eq/g tissue	–	–	–	–	0.019 ± 0.004	0.023 ± 0.005	–	–
% AD					<0.01	<0.01		
Skin								
µg eq/g tissue	0.002 ± 0.002	0.018 ± 0.005	0.116 ± 0.086	0.081 ± 0.094	0.004 ± 0.003	0.024 ± 0.007	NQ	0.006 ± 0.003
% AD	0.01	0.04	0.01	0.01	0.01	0.05	NQ	0.01

	Concentration of radioactivity in tissues/organs							
	Phenyl label						Pyridine label	
	1 × 10 mg/kg bw		1 × 300 mg/kg bw		15 × 10 mg/kg bw[b]		1 × 10 mg/kg bw	
Tissue/organ	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
Spleen								
µg eq/g tissue	0.003 ± 0.001	0.003 ± 0.001	0.028 ± 0.004	NQ	0.004 ± 0.001	0.005 ± 0.001	0.001 ± 0.0	0.002 ± 0.0
% AD	<0.01	<0.01	<0.01	NQ	<0.01	<0.01	<0.01	<0.01
Thymus								
µg eq/g tissue	0.003 ± 0.001	0.002 ± 0.001	NQ	NQ	NQ	NQ	NQ	NQ
% AD	<0.01	<0.01	NQ	NQ	NQ	NQ	NQ	NQ
Uterus								
µg eq/g tissue	NA	0.003 ± 0.001	NA	NQ	NA	NQ	NA	NQ
% AD	NA	<0.01	NA	NQ	NA	NQ	NA	NQ

AD: administered dose; bw: body weight; eq: equivalents; NA: not applicable; NQ: non-quantifiable (i.e. samples with radioactivity measurements less than twice the concurrently run background); RBCs: red blood cells; UL: uniformly labelled

[a] Tissues/organs without quantifiable radioactivity in any dose group were excluded from the table.

[b] Fourteen daily doses of unlabelled fenpicoxamid followed by a single oral dose of a mixture of unlabelled fenpicoxamid and [^{14}C-phenyl-UL]fenpicoxamid.

Source: Data obtained from Table 3, pages 53–56, in Hansen et al. (2013)

Table 7. Recovery of radioactivity in tissues and excreta of rats after administration of ^{14}C-labelled fenpicoxamid

	% of administered dose recovered (± SD)							
	Phenyl label						Pyridine label	
Excreta/tissues with collection intervals (h)	1 × 10 mg/kg bw		1 × 300 mg/kg bw		15 × 10 mg/kg bw[a]		1 × 10 mg/kg bw	
	Males	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
Expired air	–	–	–	–	–	–	–	–
Cage wash	0.27 ± 0.33	0.15 ± 0.09	7.03 ± 10.12	2.37 ± 3.16	1.33 ± 1.89	NQ	0.06 ± 0.03	0.04 ± 0.03
Urine/rinse								
0–12	7.95 ± 2.84	10.76 ± 0.37	1.16 ± 0.37	2.75 ± 2.69	7.10 ± 1.62	7.57 ± 0.76	4.68 ± 0.44	5.75 ± 0.44
12–24	6.40 ± 2.13	6.49 ± 2.00	2.37 ± 1.39	0.94 ± 0.29	4.25 ± 0.72	5.93 ± 1.86	1.28 ± 0.22	1.62 ± 1.03
24–48	2.78 ± 1.03	2.66 ± 1.42	1.82 ± 1.23	0.75 ± 0.40	1.33 ± 0.36	2.62 ± 1.67	0.33 ± 0.11	1.51 ± 1.36
48–72	0.33 ± 0.14	0.21 ± 0.11	0.87 ± 0.78	0.10 ± 0.08	0.22 ± 0.04	0.26 ± 0.14	0.07 ± 0.03	0.09 ± 0.06
72–96	0.10 ± 0.06	0.06 ± 0.03	0.92 ± 1.11	0.25 ± 0.33	0.08 ± 0.03	0.06 ± 0.04	0.02 ± 0.01	0.02 ± 0.01
96–120	0.03 ± 0.0	0.04 ± 0.03	0.73 ± 1.22	0.07 ± 0.08	0.04 ± 0.01	0.03 ± 0.02	0.02 ± 0.01	0.01 ± 0

Excreta/tissues with collection intervals (h)	% of administered dose recovered (± SD)							
	Phenyl label						Pyridine label	
	1 × 10 mg/kg bw		1 × 300 mg/kg bw		15 × 10 mg/kg bw[a]		1 × 10 mg/kg bw	
	Males	Females	Males	Females	Males	Females	Males	Females
120–144	0.02 ± 0.01	0.03 ± 0.01	0.31 ± 0.35	0.02 ± 0.03	0.03 ± 0.02	0.03 ± 0.04	0.01 ± 0.01	0.01 ± 0
144–168	0.02 ± 0.01	0.02 ± 0.01	0.24 ± 0.27	0.04 ± 0.05	0.04 ± 0.03	0.04 ± 0.06	0.01 ± 0.01	0.01 ± 0
Total	17.63 ± 2.58	20.28 ± 3.63	8.43 ± 5.26	4.91 ± 3.83	13.09 ± 2.48	16.54 ± 3.03	6.43 ± 0.51	9.01 ± 1.95
Faeces								
0–24	74.89 ± 8.94	76.55 ± 12.68	72.68 ± 14.05	85.76 ± 8.45	79.70 ± 4.59	66.92 ± 13.11	73.53 ± 10.97	50.09 ± 25.17
24–48	10.20 ± 4.08	13.52 ± 9.96	8.99 ± 4.59	8.11 ± 3.72	5.75 ± 2.44	12.24 ± 5.27	12.76 ± 12.76	26.03 ± 15.08
48–72	1.64 ± 1.25	0.73 ± 0.49	0.92 ± 0.50	0.5 ± 0.67	0.55 ± 0.17	1.39 ± 1.19	0.57 ± 0.30	1.50 ± 1.0
72–96	0.17 ± 0.10	0.1 ± 0.09	0.15 ± 0.09	0.06 ± 0.09	0.08 ± 0.04	0.15 ± 0.13	0.08 ± 0.04	0.13 ± 0.13
96–120	0.17 ± 0.28	NQ	0.10 ± 0.11	0.15 ± 0.29	0.03 ± 0.01	0.04 ± 0.03	0.03 ± 0.03	0.02 ± 0.01
120–144	NQ	NQ	0.10 ± 0.12	NQ	0.01 ± 0.01	0.01 ± 0.02	NQ	0.01 ± 0.01
144–168	0.01 ± 0.01	NQ	0.07 ± 0.11	NQ	0.01 ± 0.0	NQ	0.17 ± 0.33	NQ
Total	87.08 ± 5.07	91.04 ± 5.69	83.0 ± 15.92	94.62 ± 6.12	86.14 ± 3.06	80.76 ± 7.86	87.14 ± 1.41	77.77 ± 11.01
Tissues	0.02 ± 0.01	0.05 ± 0.03	0.02 ± 0.02	0.10 ± 0.19	0.01 ± 0.01	0.06 ± 0.02	NQ	0.01 ± 0.0
Total recovery	105 ± 4.25	111 ± 5.67	98.5 ± 2.09	102 ± 1.00	101 ± 1.26	97.5 ± 5.89	93.6 ± 1.06	86.8 ± 12.07

bw: body weight; NQ: non-quantifiable (i.e. samples with radioactivity measurements less than twice the concurrently run background); SD: standard deviation; UL: uniformly labelled

[a] Fourteen daily doses of unlabelled fenpicoxamid followed by a single oral dose of a mixture of unlabelled fenpicoxamid and [^{14}C-phenyl-UL]fenpicoxamid.

Source: Data obtained from Table 3, pages 45–52, in Hansen et al. (2013)

1.2 Biotransformation

(a) In vivo studies

In rats administered radiolabelled fenpicoxamid, unchanged parent was not excreted in the urine, but was a major component of the radioactivity recovered in the faeces. In the urine of groups dosed with the phenyl label, the major metabolites were UK-2A diol with an open ring (X1236349), UK-2A diol (X696872) and unidentified metabolite 4. Another metabolite, UK-2A open ring (X737057), was seen only in the high-dose groups. In animals given the pyridine label, the two major urinary metabolites were UK-2A diol (X696872) and unidentified metabolite 2 (Table 8).

Table 8. Metabolite profile in excreta of rats dosed with ^{14}C-labelled fenpicoxamid

	% of administered dose							
	Phenyl label						Pyridine label	
	1 × 10 mg/kg bw		1 × 300 mg/kg bw		15 × 10 mg/kg bw[a]		1 × 10 mg/kg bw	
Compound	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
Urine								
Parent	–	–	–	–	–	–	–	–
UK-2A diol open ring	7.96	9.24	3.74	2.08	4.89	7.48	–	–
UK-2A diol	6.90	7.20	2.02	1.34	5.66	5.27	2.61	3.90
UK-2A open ring	–	–	0.72	0.43	–	–	–	–
Unidentified metabolite 2	–	–	–	–	–	–	3.81	5.11
Unidentified metabolite 3	–	–	0.55	0.26	–	–	–	–
Unidentified metabolite 4	2.77	3.89	1.41	0.79	2.53	3.78	–	–
Faeces[b]								
Parent	18.3	ND	49.1	52.6	51.1	34.1	38.0	29.0
UK-2A open ring	6.68	ND	–	–	9.76	7.70	9.73	9.13
UK-2A	6.13	ND	–	–	6.20	6.28	6.79	6.47
Unidentified metabolite 1	–	ND	–	–	4.87	3.43	11.6	19.5
Total unextracted radioactivity	56.0	ND	33.9	42.0	14.2	29.3	21.0	13.6
Total								
Total identified	45.97	20.3	55.58	56.45	77.61	60.83	57.13	48.5
Total unidentified[c]	58.77	91.04[d]	34.96	43.05	21.6	36.51	36.41	38.21
Total accounted for[e]	105	111	90.5	99.5	99.2	97.3	93.5	86.7
Lost/unaccounted for[f]	0	0	9	0.5	0.8	2.7	6.5	13.3

–: non-quantifiable (i.e. samples with radioactivity measurements less than twice the concurrently run background); bw: body weight; ND: no data; UL: uniformly labelled

[a] Fourteen daily doses of unlabelled fenpicoxamid followed by a single oral dose of a mixture of unlabelled fenpicoxamid and [^{14}C-phenyl-UL]fenpicoxamid.

[b] No faeces data for low-dose single-dose [^{14}C-phenyl-UL]fenpicoxamid females due to low recoveries of radioactivity from faecal homogenate extracts.

[c] Total unidentified = (unidentified metabolites) + (total unextracted radioactivity).

[d] Total unidentified for low-dose single-dose [^{14}C-phenyl-UL]fenpicoxamid females was assumed to be equivalent to the percentage of administered dose in faeces, as presented in Table 7 above.

[e] Total accounted for = (total identified) + (total unidentified).

[f] 100 − (total accounted for).

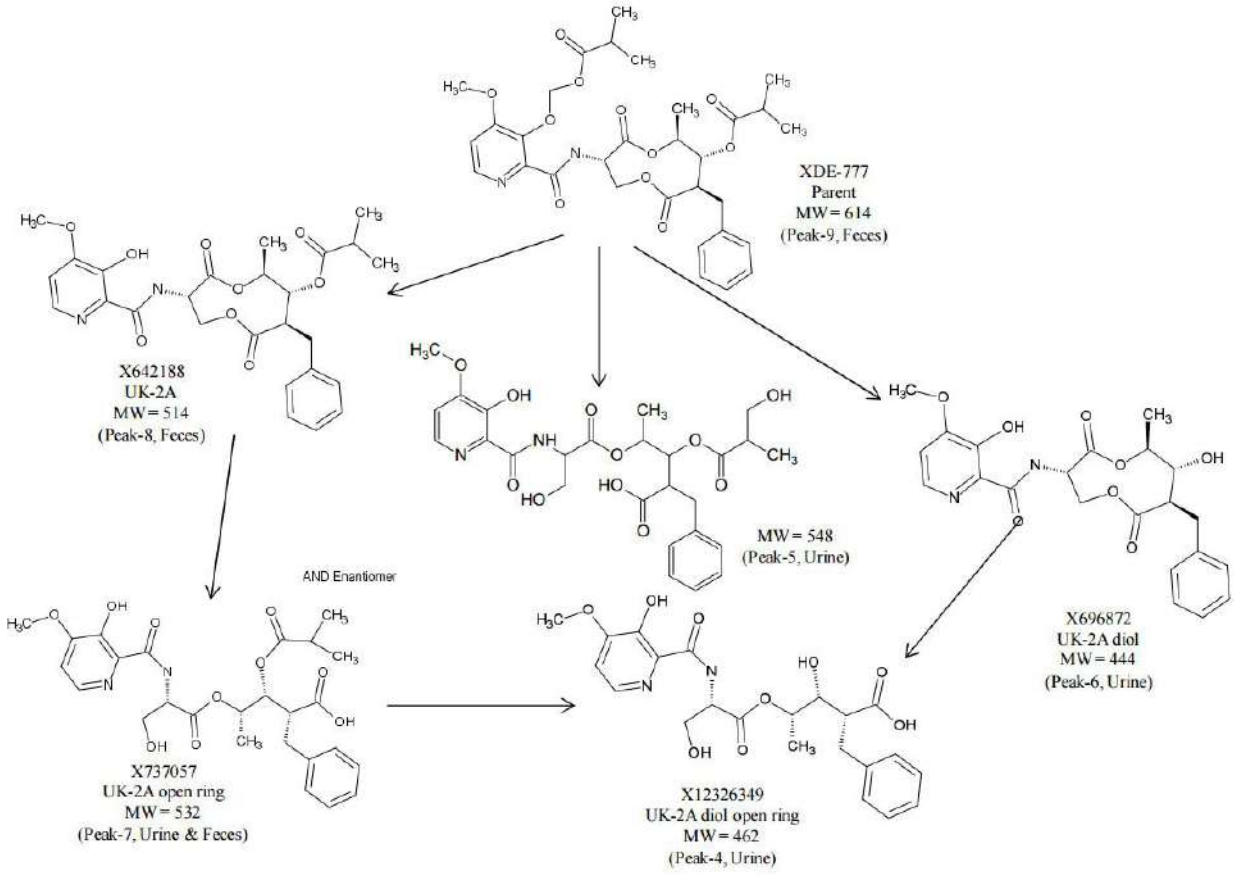
Source: Data obtained from Table 2, page 145, in Hansen et al. (2013)

Although the largest percentage of recovered radioactivity in the faeces was identified as unchanged parent, a large portion, regardless of dose or label, was unextracted radioactivity (Table 8). The unextracted radioactivity represents the fraction of the administered dose that became irreversibly

bound within the faeces and may contribute to the low apparent absorption of fenpicoxamid. This bound fraction is lowest in the repeated-dose groups, and there are sex differences that may account for durational effects and sex differences seen in the database. This apparent overwhelming of the faecal binding seen in the repeated-dose metabolism study may relate to durational effects in the remainder of the database. Relative availability of fenpicoxamid is described in the toxicokinetics from individual studies compiled in section 1.3 below.

The proposed metabolic pathway for fenpicoxamid in rats is shown in Fig. 3. The principal routes of metabolism of fenpicoxamid involved hydrolysis of various ester groups, as well as *O*-dealkylation of the hydroxymethoxy side-chain of the pyridine ring.

Fig. 3. Proposed metabolic pathway for fenpicoxamid in rats



Source: Hansen et al. (2013)

(b) In vitro studies

In an in vitro comparative metabolism study, rat, mouse and human liver microsomes were exposed to a 0.065 µmol/L concentration of fenpicoxamid (purity 79.4%) and [^{14}C-2-pyridine]fenpicoxamid (radiopurity 99.1%). Owing to the low concentrations and an excess of enzyme activity in all three species, the study did not inform on species-specific total capacity to metabolize the parent compound. Qualitative differences between the species were identified.

The parent was identified only in the microsome-free incubations, indicating that all three species were capable of metabolism. Eight metabolites were detected, although only X1236349 and X737057 were identified. Three metabolites, including X1236349, were detected in the absence of microsomes, indicating that they are impurities of the test substance when detected at those levels.

The human microsome incubations formed only three substances as metabolites, “d”, “e” and X737057. All three species formed “e” at comparable levels of approximately 25% of the applied dose. Metabolite “d” was found in the human microsome incubations at approximately 3% of the applied dose, but in the mouse microsome incubations at approximately 15% of the applied dose. X737057 was found in the human microsome incubations at higher levels than in the rat microsome incubations (~21% in humans versus ~11% in rats). Both the rat and mouse microsome incubations formed metabolite “a”, a very polar metabolite (~8–12% of the applied dose over background), whereas metabolite “b” was found only in the mouse microsome incubations, and metabolites “c” and “g” (both ~1% of the applied dose) were found only in the rat microsome incubations. The presence of metabolite “g” at background levels in the rat microsome incubations suggests that it is an impurity; however, its absence in the mouse and human microsome incubations suggests that it can be metabolized into another product. Microsomal protein precipitate was noted and accounted for approximately 10% of the unextracted label, suggesting label binding (Zhang et al., 2014).

1.3 Toxicokinetics

Urine and blood samples were taken from a representative sample of the toxicity studies to confirm the steady-state systemic concentrations of fenpicoxamid as described in section 1.1 above and to confirm levels of internal exposure to the test substance.

Toxicokinetic analysis was performed in three mouse studies. In a 28-day dietary study, blood concentrations of the parent compound were too low to allow an analysis to be performed. Concentrations of metabolite X737057 in the blood were sublinear at the high dose (6000 parts per million [ppm]) in females and at the middle dose (3000 ppm) in males. Urinary concentrations of fenpicoxamid were above the lower level of quantification (LLQ) in all dose groups in males and above the LLQ in females at the middle and high doses. In male mice, concentrations of the parent compound were sublinear at the middle dose, whereas concentrations were linear in females. Urinary concentrations of metabolite X737057 were equivalent to those of the parent compound in males and 4.5 times higher than those of the parent compound in females. Both sexes exhibited non-linear concentrations at the middle dose for the metabolite (Thomas, Murray & McCoy, 2012).

In a 90-day dietary study, fenpicoxamid was present in the blood above the LLQ in females but not in males, whereas it was present in urine above the LLQ in males but not in females, indicating separate and more efficient pathways in males. Metabolite X737057 was found in both blood and urine of males and females. Blood fenpicoxamid concentrations were statistically linear but visually non-linear at the low–middle dose (1500 ppm) in females. Urinary fenpicoxamid concentrations were sublinear at the high dose (6000/9000 ppm) in males. Blood concentrations of metabolite X737057 were 17% and 65% of the blood concentrations of fenpicoxamid in females given the low (300 ppm) and high doses (6000 ppm), respectively. Blood concentrations were less than proportional at the higher doses, with the inflection point at the middle–high dose (3000 ppm) in males and females. Urinary concentrations of metabolite X737057 were non-linear at the high dose in males and statistically linear, but visually non-linear, at the middle–high dose in females (Thomas, Murray & McCoy, 2014).

Concentration analyses in an 18-month study revealed that fenpicoxamid was rapidly metabolized and/or excreted and was not present at quantifiable levels in the majority of blood and urine samples collected after 3, 6 and 12 months of treatment. However, the major metabolite, X12326349, and a lesser metabolite, X737057, were both present at quantifiable levels in most samples obtained from treated animals. Dose proportionality in the blood and urine was inconsistent for metabolite X12326349 at 3 and 6 months. At 12 months, levels of metabolite X12326349 in the blood were dose proportionate; however, test substance intake was decreased. In the urine, excretion was higher at 12 months than at 3 and 6 months; however, dose proportionality was regained (Thomas, Murray & McCoy, 2013).

Overall, the data from the three mouse studies suggest that there are changes in the kinetics of fenpicoxamid and its metabolites over time and that this change in kinetics may be complicated by

multiple, possibly competing, mechanisms of non-linearity. Levels of the minor metabolite, X737057, were more likely to be less than dose proportionate in the blood, but linear in urinary excretion (Thomas, Murray & McCoy, 2012, 2013, 2014).

In the 28-day, 90-day and 1-year dog studies, blood concentrations of fenpicoxamid and its two metabolites, X737057 and X12326349, were generally low. Where analysis of the AUC was possible, blood concentrations were statistically linear, but visually non-linear, with plateaus at the highest doses administered. Urinary concentrations accounted for less than 0.1% of the administered dose in all studies, including the 1-year study, where urinary elimination of parent compound, metabolite X737057 and metabolite X12326349 accounted for less than 0.01%, less than 0.05% and less than 0.07% of the administered dose, respectively, regardless of the dose. Analysis of urinary elimination was possible only for metabolite X737057 in the 28-day study, where it was sublinear. In the 90-day study, urinary elimination was linear for the parent compound, statistically but visually non-linear for metabolite X12326349 and, for metabolite X737057, non-linear at the top dose for males and statistically linear, but visually non-linear, in females (Heward, 2013a,b, 2014).

Toxicokinetics were evaluated in rats in the 29-day, 90-day (diurnal variation assessment) and 2-year dietary toxicity studies as well as in the reproductive toxicity study and developmental toxicity study. In the short-term and long-term toxicity studies, blood concentrations of fenpicoxamid were low to undetectable. Urinary concentrations were generally higher, non-linear over a shorter duration of dosing and linear in the 90-day and 2-year studies. Samples were analysed for metabolite X737057 in all studies. Blood concentrations after 29 days were dose dependent in males but not in females. After 90 days, blood concentrations were non-linear in males at the middle (6000 ppm) and high doses (11 500/14 000 ppm) and statistically linear, but visually non-linear, in females at the same doses. Neither of the metabolites in the 2-year study, X737057 and X12326349, showed linearity of blood concentrations; however, the point of departure for blood linearity was unclear in the absence of dosing below 100 mg/kg bw per day. Urinary concentrations of metabolite X737057 were higher than blood concentrations, but did not follow a linear increase pattern after 29 or 90 days of exposure. In the 2-year study, concentrations of metabolites X12326349 and X737057 in the urine were visually non-linear at the middle dose (10 000 ppm) and high doses (30 000 ppm) and statistically non-linear at the high dose. It was noted that the low blood concentrations of the parent compound and two metabolites and shallow dose–response curves indicate that there was little internal exposure (Stebbins, Murray & McCoy, 2012; Stebbins et al., 2012, 2014).

In the preliminary reproductive toxicity study in rats, the fenpicoxamid concentration in blood was below the LLQ in all doses in males and sublinear at the middle dose (9000 ppm) in females. Concentrations of the parent compound were sublinear in milk at the low dose (4500 ppm). Fenpicoxamid was isolated in the blood of pups, but there was evidence of cross-contamination, and the results were considered unreliable. Metabolite X737057 was found in males, females, offspring and milk. Concentrations were sublinear in adults and milk, but linear in pups. Although the levels of the metabolite were higher than the levels of the parent compound in the blood of adults, they were lower than fenpicoxamid levels in the milk (Rasoulpour et al., 2012a).

In the preliminary developmental toxicity study in rats, only plasma was investigated. Fenpicoxamid was undetected in dams and fetuses, whereas metabolite X737057 was found in dams and fetuses, and at comparable levels in both. In dams, the concentrations were sublinear between the low (4500 ppm) and middle doses (9000 ppm), although they were effectively linear in fetuses. Concentrations of the metabolite were 6- to 10-fold higher than in the main study, in which whole blood was analysed. In the main study, fenpicoxamid was not found above the LLQ in the dams, but was found in two of the 12 fetal samples from treated groups. The samples were analysed for both metabolites X12326349 and X737057, which were found above the LLQ in both dams and fetuses. Metabolite X12326349 was found at higher concentrations than metabolite X737057, and fetal concentrations were approximately 76% and 32% of the maternal blood levels, respectively. Blood levels of metabolite X737057 were sublinear at the middle dose, whereas levels of metabolite X12326349 were statistically linear, but visually non-linear, at the high dose (13 500 ppm) (Rasoulpour et al., 2012b).

In the preliminary developmental toxicity study in rabbits, only the low-dose (12 250 ppm) animals were sampled. Concentrations of metabolite X12326349 were found to be above the LLQ; however, the parent compound was found at trace levels in two of the five samples, and metabolite X737057 was not found in any of the samples. In the main study, neither fenpicoxamid nor metabolite X737057 was found above the LLQ in does or fetuses. Metabolite X12326349 was found in the blood samples of both. Metabolite concentrations in the fetal and maternal samples were statistically linear and visually non-linear. Whereas metabolite concentrations in maternal and fetal samples were roughly equal at 5000 and 15 000 ppm, fetal concentrations at the low dose were approximately 28% of those of the maternal animals (Rasoulpour et al., 2012c; Ellis-Hutchings, Bell & McCoy, 2013).

Overall, the low internal exposure, as evidenced by low levels of fenpicoxamid and the major metabolites in the samples, and lack of linearity in many of the studies mean that less weight can be placed on the dose–response relationship.

2. Toxicological studies

2.1 Acute toxicity

(a) Lethal doses

In an acute oral toxicity study, rats were given a limit dose of fenpicoxamid (purity 78.0%) in 0.5% methylcellulose in distilled water at 2000 mg/kg bw. There were no mortalities and no clinical signs of toxicity. Body weights decreased in two animals between day 7 and day 14, although all other animals gained weight throughout the study. There were no gross changes at necropsy (Durando, 2011a).

In an acute dermal toxicity study, rats were given a limit dose of fenpicoxamid (purity 78.0%) moistened with 0.5% methylcellulose in distilled water at 5000 mg/kg bw for 24 hours. There were no mortalities and no signs of systemic toxicity. Yellow staining was noted at the test site in both males and females. One male and one female each either lost weight or did not gain weight in the first week of observation; however, all animals gained weight by the end of the observation period. There were no gross changes at necropsy (Durando, 2011b).

In an acute inhalation study, rats were given a maximum achievable concentration of fenpicoxamid (purity 78.0%) at 0.53 mg/L for 4 hours. There were no mortalities. Clinical signs of toxicity were limited to periocular staining in one female on day 14 and day 15. Body weights were decreased following exposure; however, all animals gained weight from day 4 until the end of the observation period. There were no gross changes at necropsy (Krieger & Garlinghouse, 2012).

Fenpicoxamid is therefore of low acute oral and dermal toxicity and slight inhalation toxicity in rats (Table 9).

Table 9. Acute toxicity of fenpicoxamid

Species	Strain	Sex	Route	Purity (%)	Result	Reference
Rat	F344	Female	Oral	78.0	LD_{50} > 2 000 mg/kg bw	Durando (2011a)
Rat	F344	Male and female	Dermal	78.0	LD_{50} > 5 000 mg/kg bw	Durando (2011b)
Rat	F344	Male and female	Inhalation	78.0	LC_{50} > 0.53 mg/L	Krieger & Garlinghouse (2012)

bw: body weight; LC_{50}: median lethal concentration; LD_{50}: median lethal dose

(b) Dermal irritation

In a dermal irritation study, 0.5 mg of fenpicoxamid (purity 78.0%) was moistened with 0.5% methylcellulose in water and applied on a 2.5 cm × 2.5 cm gauze patch to the skin of three male New Zealand white rabbits for 4 hours. Very slight erythema was noted at the test site in one of the three animals, and no oedema was noted. All scores at the 24-, 48- and 72-hour marks were zero. Fenpicoxamid is considered to be non-irritating to the skin of rabbits (Durando, 2011c).

(c) Ocular irritation

In an eye irritation study, 0.04–0.05 g of fenpicoxamid (purity 78.0%) was instilled into the conjunctival sac of one eye of three female New Zealand white rabbits. The eyes were left unwashed following instillation, and the opposite eyes were left as controls. Slight to marked redness, slight chemosis and slight to marked discharge were noted in all animals. All signs of irritation had abated by 72 hours. Fenpicoxamid is considered to be minimally irritating to the eyes of rabbits based on persistence of irritation past 24 hours (Durando, 2011d).

(d) Dermal sensitization

In a dermal sensitization study using a local lymph node assay, five female CBA/J mice per dose were exposed to three daily applications of 0%, 5%, 25% or 75% fenpicoxamid (purity 78.0%) in dimethyl sulfoxide for 3 consecutive days. Following intravenous injection of 740 kBq of ^{3}H-labelled thymidine, individual animal disintegrations per minute counts were obtained, and the stimulation index was calculated for each dose group. The stimulation indices for the 5%, 25% and 75% groups were 0.9, 1.2 and 1.3, respectively. A concurrent positive control assay was performed with α-hexylcinnamaldehyde, which validated the study. Fenpicoxamid is not considered to be a dermal sensitizer in mice (Boverhof & Sosinski, 2012).

(e) Phototoxicity

In an in vitro 3T3 NRU phototoxicity test, mouse BALB/c 3T3 cells cultured in vitro were exposed to fenpicoxamid (purity 84.2%) dissolved in dimethyl sulfoxide. Concentrations of 0.244, 0.488, 0.977, 1.953, 3.906, 7.813, 15.63 and 31.25 µg/mL were investigated in the presence and absence of artificial sunlight irradiance. A mean phototoxic effect (MPE) of 0.061 was recorded, which corresponded with no phototoxic potential predicted (i.e. MPE < 0.1). Similarly, photo-irritancy factor data did not fall in the phototoxic range. No cytotoxic effects were observed after treatment of cells in either the presence or the absence of artificial sunlight. The positive controls induced the appropriate response. There was no evidence that fenpicoxamid had any phototoxic effects on BALB/c 3T3 cells (Roth, 2015).

2.2 Short-term studies of toxicity

(a) Oral administration

Mice

In a 7-day palatability study, groups of three female Crl:CD1 (ICR) mice received fenpicoxamid (purity 78.0%) in the diet at a concentration of 0, 1432, 2864 or 5727 ppm (equal to 0, 286, 584 and 1164 mg/kg bw per day, respectively). Animals were monitored daily for general health, significant clinical abnormalities, body weight, body weight gain and feed consumption. Animals were killed on day 7, with the exception of control animals, which were returned to the vivarium, and a gross necropsy was performed.

There were no mortalities. There were no effects on body weight or feed consumption, and body weight gains in the high-dose group were slightly higher than those of controls. Mesenteric lymph nodes were increased in size in one mid-dose and two high-dose animals, and renal lymph nodes were increased in size in one high-dose animal. Peyer's patches were of increased prominence throughout the gastrointestinal tract of one high-dose animal (Thomas, Murray & Sura, 2010).

In a 28-day toxicity study, groups of five Crl:CD1 (ICR) mice received fenpicoxamid (purity 78.0%) in the diet at a concentration of 0, 1923, 3846 or 7692 ppm (0, 1500, 3000 and 6000 ppm, corrected for test substance purity; equal to 0, 216, 444 and 901 mg/kg bw per day for males and 0, 295, 652 and 1177 mg/kg bw per day for females, respectively). Animals were monitored twice daily for mortality and moribundity and daily for clinical signs of toxicity. Cage-side observations were performed daily, and detailed clinical observations were performed weekly. Body weight, body weight gain and feed consumption were measured twice in the first week and weekly thereafter. Ophthalmological examinations were performed pre-exposure and prior to scheduled necropsy. Haematology and clinical chemistry parameters were analysed from samples taken prior to terminal kill, and toxicokinetics was analysed in urine and whole blood. Gross examinations were performed, organs were weighed and histopathological examination was performed on animals from the control and high-dose groups, including the one high-dose male that died during the study.

There was one mortality attributed to the stress of handling. There were no treatment-related effects on clinical signs, body weight, feed consumption, ophthalmology, haematology parameters or gross pathological observations.

Changes to the adrenal glands consisted of increased weights at and above 3000 ppm in males and in all treated groups in females. There was an increase in the incidence of very slight hypertrophy of the zona fasciculata at and above 3000 ppm in females and at 6000 ppm in males. As there were no histopathological adrenal changes in the 90-day study (see below) at similar doses and in larger dose groups, these changes were considered equivocal.

Changes in the liver consisted of increased liver weights in males at 3000 and 6000 ppm. In females, liver weights were increased at 1500 ppm; however, as the dose increased, the extent of the liver weight increase was less compared with controls. The incidence of slight hepatocellular hypertrophy was increased at 3000 and 6000 ppm in males and females. Blood albumin concentrations were decreased in females in all treated groups. Liver changes were consistent with those seen in the 90-day toxicity study (see below) (Thomas, Murray & McCoy, 2012).

In a 90-day toxicity study, groups of 10 Crl:CD1 (ICR) mice received fenpicoxamid (purity 78.0%) in the diet at a concentration (corrected for purity) of 0, 300, 1500, 3000 or 6000/9000 ppm (increased at day 57) (equal to 0, 40, 192, 399 and 921 mg/kg bw per day, respectively) for males and 0, 300, 1500, 3000 or 6000 ppm (equal to 0, 49, 303, 566 and 1107 mg/kg bw per day, respectively) for females. Additional groups of 10 animals received 0 and 3000/6000 ppm for males and 0 and 6000 ppm for females for 90 days and were given untreated diet for an additional 28-day recovery period. Animals were monitored twice daily for mortality and moribundity and daily for clinical signs of toxicity. Cage-side observations were performed daily, and detailed clinical observations were performed weekly. Body weight, body weight gain and feed consumption were measured twice in the first week and weekly thereafter. Ophthalmological examinations were performed pre-exposure and prior to scheduled necropsy. Haematology and clinical chemistry parameters were analysed from samples taken prior to terminal kill, and toxicokinetics was analysed in urine and whole blood. Gross examinations were performed, organs were weighed and histopathological examination was performed on animals from the control and high-dose groups.

There were no effects on mortality, clinical signs of toxicity, body weight, body weight gain, feed consumption, ophthalmology or haematology. Changes were limited to the liver at and above 1500 ppm, with increased organ weight and hepatocellular hypertrophy with altered tinctorial properties in males and females, decreased serum triglycerides, increased hepatocyte fatty change and

multifocal single-cell necrosis in males and decreased serum albumin in females. At 3000 ppm, serum albumin was decreased in males. At 6000 ppm, serum total protein and cholesterol were decreased in females. There were no treatment-related changes following the 28-day recovery period.

The no-observed-adverse-effect level (NOAEL) was 300 ppm (equal to 40 mg/kg bw per day), based on increased liver weights and hepatocellular hypertrophy in males and females, decreased serum triglycerides, hepatocyte fatty change and multifocal single-cell necrosis in males and decreased serum albumin in females at 1500 ppm (equal to 192 mg/kg bw per day) (Thomas, Murray & McCoy, 2014).

Rats

In a 7-day palatability study, groups of three female F344/DuCrl rats received fenpicoxamid (purity 78.0%) at a concentration of 0, 2269, 4537 or 9074 ppm (equal to 0, 246, 473 and 1000 mg/kg bw per day, respectively, corrected for test material purity). Animals were monitored daily for general health, significant clinical abnormalities, body weight, body weight gain and feed consumption. Animals were killed on day 7, with the exception of control animals, which were returned to the vivarium, and a gross necropsy was performed.

There were no effects on mortality, clinical signs of toxicity, body weight, body weight gain, feed consumption or gross necropsy (Sura & Murray, 2010).

In a 29-day toxicity study, groups of five F344/DuCrl rats of each sex received fenpicoxamid (purity 78.0%) at a concentration of 0, 2949, 5769 or 11 538 ppm (0, 2300, 4500 and 9000 ppm, corrected for test material purity; equal to 0, 196, 395 and 788 mg/kg bw per day for males and 0, 197, 377 and 764 mg/kg bw per day for females, respectively). Animals were monitored twice daily for mortality and moribundity and daily for clinical signs of toxicity. Cage-side observations were performed daily, and detailed clinical observations were performed weekly. Body weight, body weight gain and feed consumption were measured twice in the first week and weekly thereafter. Ophthalmological examinations were performed pre-exposure and prior to scheduled necropsy. Haematology and clinical chemistry parameters were analysed from fasted samples taken prior to terminal kill, and urine analysis was performed on samples taken from the metabolism cages the week prior to terminal kill. Urinary sediment was characterized from pooled samples. Toxicokinetics was analysed in urine and whole blood. Gross examinations were performed, organs were weighed and histopathological examination was performed on animals from the control and high-dose groups and on gross lesions in all dose groups.

There were no effects on mortality, clinical signs of toxicity, body weight, body weight gain, feed consumption, haematology, organ weights, gross pathology or histopathology. At 9000 ppm, cholesterol was increased in males and females, urine volume was increased in females and specific gravity was decreased in females; however, owing to the lack of a dose–response relationship, the adversity and relationship to treatment were unknown.

The NOAEL was 9000 ppm (equal to 764 mg/kg bw per day), the highest dose tested (Stebbins, Murray & McCoy, 2012).

In a 90-day toxicity study, groups of 15 F344/DuCrl rats of each sex received fenpicoxamid (purity 78.0%) at a dietary concentration of 0, 3000, 6000 or 11 500/14 000 ppm (dose increased at day 71) (corrected for test material purity; equal to 0, 180, 365 and 732 mg/kg bw per day for males and 0, 205, 413 and 834 mg/kg bw per day for females, respectively). Animals were monitored twice daily for mortality and moribundity and daily for clinical signs of toxicity. Cage-side observations were performed daily, and detailed clinical observations were performed weekly. Body weight, body weight gain and feed consumption were measured twice in the first week and weekly thereafter.

Ophthalmological examinations were performed pre-exposure and prior to scheduled necropsy. Haematology and clinical chemistry parameters were analysed from fasted samples taken prior to terminal kill, and urine analysis was performed on samples taken from the metabolism cages the week prior to terminal kill. Urinary sediment was characterized from pooled samples. Toxicokinetics was analysed in urine and whole blood. Gross examinations were performed, organs were weighed and histopathological examination was performed on animals from the control and high-dose groups and on gross lesions in all dose groups. Five animals of each sex per group were subjected to neurobehavioural examination in all dose groups and to neurohistopathology in the control and high-dose groups.

There were no effects on mortality, clinical signs of toxicity, body weight, body weight gain, feed consumption, haematology, clinical chemistry, organ weights, gross pathology or histopathology. There were no effects in the neurological subgroups.

The NOAEL was 11 500/14 000 ppm (equal to 732 mg/kg bw per day), the highest dose tested (Stebbins et al., 2012).

Dogs

In a 5-day palatability study, groups of two female beagle dogs received fenpicoxamid (purity 79.4%) at a dietary concentration of 0, 15 000 or 30 000 ppm (equivalent to 0, 375 and 750 mg/kg bw per day), and a group of two male beagle dogs received fenpicoxamid (purity 78.0%) at a dietary concentration of 30 000 ppm (equivalent to 750 mg/kg bw per day). Animals were observed for morbidity, mortality, injury, body weight and feed consumption twice daily and for clinical signs daily. At the end of the palatability study, animals were subjected to a 3-week washout period and transferred into the 28-day oral toxicity study.

Feed consumption and body weights were slightly decreased in the first day or two of exposure in all treated animals. Both had returned to levels comparable to control values by the second day (Heward, 2012).

In a 28-day toxicity study, groups of two female beagle dogs received fenpicoxamid (purity 79.4%) at a dietary concentration of 0, 15 000 or 30 000 ppm (equal to 0, 446.1 and 1110.1 mg/kg bw per day, respectively; 0, 354 and 881 mg/kg bw per day, respectively, corrected for test substance purity), and a group of two male beagle dogs received fenpicoxamid (purity 78.0%) at a concentration of 30 000 ppm (equal to 915.9 mg/kg bw per day; 727 mg/kg bw per day, corrected for purity). Animals were observed for morbidity, mortality and injury twice daily and for clinical signs daily. Body weight and feed consumption were measured weekly. Ophthalmoscopic examinations were conducted and haematology and clinical chemistry parameters were measured pretest and prior to terminal necropsy. Urine analysis was performed in week 4. Gross pathological and histopathological examinations were carried out in all groups, and organ weights were measured in all groups.

There were no effects on mortality or clinical signs of toxicity. Males and females in the 30 000 ppm group lost body weight during the study, and one of two females in the 15 000 ppm group lost body weight. Feed consumption was decreased in the first week of treatment in one male and one female given 30 000 ppm. There were no effects on ophthalmology, haematology, clinical chemistry or urine analysis parameters. There were no effects on gross pathology, histopathology or organ weights (Heward, 2013a).

In a 90-day toxicity study, groups of four beagle dogs of each sex received fenpicoxamid (purity 79.4%) at a dietary concentration of 0, 3000, 10 000 or 30 000 ppm (corrected for test material purity; equal to 0, 100, 408 and 939 mg/kg bw per day for males and 0, 122, 353 and 1115 mg/kg bw per day for females, respectively). Animals were observed for morbidity, mortality and injury twice daily and for clinical signs weekly. Body weight and feed consumption were measured daily for the

first 2 weeks of the study and weekly thereafter. Ophthalmoscopic examinations were performed in the pretest period and prior to scheduled necropsy. Haematology, clinical chemistry and urine analysis parameters were measured pretest and at weeks 7 and 13. Gross pathological and histopathological examinations were performed in all groups, and organ weights were measured in all groups.

There were no effects on mortality, body weight, body weight gain, feed consumption, haematology, clinical chemistry or urine analysis parameters, gross pathological or histopathological examinations or organ weights.

The NOAEL was 30 000 ppm (equal to 939 mg/kg bw per day), the highest dose tested (Heward, 2013b).

In a 1-year toxicity study, groups of four beagle dogs of each sex received fenpicoxamid (purity 79.4% in weeks 1–28 and 83.7% in weeks 29–52) at a dietary concentration of 0, 3000, 10 000 or 30 000 ppm (equal to 0, 84, 300 and 981 mg/kg bw per day for males and 0, 80, 273 and 1011 mg/kg bw per day for females, respectively, corrected for test substance purity). Animals were observed for morbidity, mortality and injury twice daily and for clinical signs weekly. Body weight and feed consumption were measured weekly, with the exception of twice during week 2 during a period of low feed consumption. Ophthalmoscopic examinations were performed in the pretest period and prior to scheduled necropsy. Haematology, clinical chemistry and urine analysis parameters were measured pretest and at 3, 6, 9 and 12 months. Faecal samples were examined for ova and parasites 3 months into the study period. Gross pathological and histopathological examinations were performed in all groups, and organ weights were measured in all groups.

There were no effects on mortality, ophthalmology, haematology or urine analysis parameters or gross pathology. Clinical signs of toxicity consisted of an increased incidence of thin appearance at 10 000 ppm and above in both males and females. Overall body weight was decreased compared with controls in males starting at 10 000 ppm, and males exhibited a week of body weight loss at and above 10 000 ppm and reduced body weight gain thereafter. Body weights were decreased in females at 30 000 ppm. Total bilirubin was increased in males and females at 10 000 ppm, and relative liver weights were increased in males in all treated groups. Hepatocellular hypertrophy was increased in males at 10 000 ppm (Table 10). The combined effect on liver parameters was considered adverse at 10 000 ppm in males.

Table 10. Effects in the 1-year oral toxicity study in dogs

	Males				**Females**			
	0 ppm	**3 000 ppm**	**10 000 ppm**	**30 000 ppm**	**0 ppm**	**3 000 ppm**	**10 000 ppm**	**30 000 ppm**
Clinical signs								
Excretion								
Faeces discoloured, red	0/0[a]	0/0	0/0	1/1	1/1	0/0	0/0	0/0
Faeces, mucoid	2/1	0/0	0/0	1/1	5/3	3/2	1/1	2/1
Faeces, soft	181/4	600/4	583/4	889/4	72/4	139/4	231/4	491/4
Faeces, watery	14/4	257/4	279/4	447/4	1/1	0/0	78/2	63/4
External appearance								

	Males				Females			
	0 ppm	**3 000 ppm**	**10 000 ppm**	**30 000 ppm**	**0 ppm**	**3 000 ppm**	**10 000 ppm**	**30 000 ppm**
Thin	0/0	0/0	87/3	248/2	5/1	0/0	20/1	235/2
Body weight (kg)								
Day −1	8.21 ± 1.17	8.14 ± 0.77	8.60 ± 0.81	8.68 ± 1.00	8.05 ± 0.72	7.79 ± 0.89	7.99 ± 1.04	7.86 ± 0.46
Day 7	8.30 ± 1.19	8.14 ± 0.73	8.34 ± 0.94	8.28 ± 1.08	7.89 ± 0.61	7.85 ± 0.87	7.65 ± 1.12	7.36 ± 0.63
Day 14	8.29 ± 1.33	8.22 ± 0.85	8.36 ± 0.99	8.19 ± 1.03	7.80 ± 0.66	7.96 ± 0.89	7.54 ± 1.16	7.46 ± 0.52
Day 28	8.50 ± 1.17	8.23 ± 0.65	8.21 ± 1.14	7.96 ± 0.93 (−6.4%)	7.85 ± 0.76	8.21 ± 0.82	7.55 ± 1.23	7.54 ± 0.24
Day 42	8.71 ± 1.23	8.33 ± 0.75	8.31 ± 1.10	8.04 ± 0.74 (−7.7%)	7.86 ± 0.96	8.35 ± 0.62	7.74 ± 1.17	7.71 ± 0.35
Day 56	8.93 ± 1.19	8.43 ± 0.69	8.29 ± 1.07 (−7.2%)	8.00 ± 0.83 (−10.4%)	7.60 ± 1.18	8.46 ± 0.63	7.73 ± 1.20	7.65 ± 0.44
Day 70	9.00 ± 1.09	8.56 ± 0.64	8.28 ± 1.17 (−8.0%)	8.05 ± 0.74 (−10.6%)	7.65 ± 1.51	8.51 ± 0.60	7.69 ± 1.31	7.44 ± 0.42
Day 84	9.09 ± 0.97	8.46 ± 0.58 (−6.9%)	8.21 ± 1.15 (−9.7%)	8.14 ± 0.70 (−10.5%)	7.58 ± 1.38	8.35 ± 0.64	7.76 ± 1.29	7.40 ± 0.32
Day 98	9.18 ± 1.03	8.49 ± 0.50 (−7.5%)	8.26 ± 1.00 (−10.0%)	8.26 ± 0.66 (−10.0%)	7.69 ± 1.22	8.38 ± 0.49	7.76 ± 1.30	7.35 ± 0.32
Day 196	9.80 ± 0.87	9.03 ± 0.70 (−7.9%)	8.71 ± 1.11 (−11.1%)	8.83 ± 0.42 (−9.9%)	8.43 ± 1.68	8.74 ± 0.42	8.38 ± 1.60	7.85 ± 0.72 (−6.9%)
Day 210	9.78 ± 0.82	9.10 ± 0.67 (−7.0%)	8.79 ± 1.11 (−10.1%)	8.90 ± 0.54 (−9.0%)	8.60 ± 1.74	8.80 ± 0.35	8.45 ± 1.67	7.89 ± 0.59 (−8.3%)
Day 364	10.01 ± 0.54	9.36 ± 0.94 (−6.5%)	8.86 ± 0.94 (−11.5%)	9.35 ± 0.47 (−6.6%)	9.20 ± 2.28	8.91 ± 0.45	8.75 ± 1.60	8.16 ± 0.90 (−11.3%)
Body weight gain (kg)	1.8	1.22	0.26	0.67	1.15	1.12	0.76	0.30
Clinical chemistry								
Total bilirubin (mg/dL)								
Pretest	0.18 ± 0.050	0.18 ± 0.050	0.15 ± 0.058	0.15 ± 0.058	0.15 ± 0.058	0.18 ± 0.050	0.18 ± 0.050	0.18 ± 0.050
3 months	0.15 ± 0.058	0. 20 ± 0.000	0.30 ± 0.000	0.38 ± 0.050	0.20 ± 0.000	0.30 ± 0.000	0.33 ± 0.050	0.40 ± 0.082
6 months	0.20 ± 0.000	0.28 ± 0.050	0.35 ± 0.058	0.45 ± 0.058	0.23 ± 0.050	0.30 ± 0.000	0.38 ± 0.050	0.50 ± 0.000
9 months	0.20 ± 0.000	0.25 ± 0.058	0.35 ± 0.058	0.50 ± 0.000	0.20 ± 0.000	0.28 ± 0.050	0.35 ± 0.058	0.55 ± 0.100

	Males				Females			
	0 ppm	**3 000 ppm**	**10 000 ppm**	**30 000 ppm**	**0 ppm**	**3 000 ppm**	**10 000 ppm**	**30 000 ppm**
12 months	0.18 ± 0.050	0.25 ± 0.058	0.38 ± 0.050	0.50 ± 0.000	0.20 ± 0.000	0.25 ± 0.058	0.38 ± 0.050	0.50 ± 0.000
Organ weights								
Liver								
Absolute (g)	243 ± 25	261 ± 41 (7%)	251 ± 44 (3%)	278 ± 20 (14%)	217 ± 15	216 ± 16	209 ± 37	226 ± 27
Relative (%)	2.47 ± 0.11	2.85 ± 0.19** (15%)	2.90 ± 0.17** (17%)	3.13 ± 0.12** (27%)	2.58 ± 0.64	2.48 ± 0.17	2.48 ± 0.10	2.94 ± 0.36
Histopathology								
Hypertrophy, with altered tinctorial properties, hepatocyte, panlobular – very slight	0	1	4	3	0	0	0	0

ppm: parts per million; **: $P < 0.01$ (statistical analysis performed only on organ weights)
[a] Number of times observed/total number of animals affected.
Source: Heward (2014)

The NOAEL was 3000 ppm (equal to 80 mg/kg bw per day), based on an increased incidence of thin appearance and increased total bilirubin in males and females and decreased body weight and increased liver changes in males at 10 000 ppm (equal to 273 mg/kg bw per day) (Heward, 2014).

(b) Dermal application

No studies were submitted.

(c) Exposure by inhalation

No studies were submitted.

2.3 Long-term studies of toxicity and carcinogenicity

Mice

In an 18-month carcinogenicity study, groups of 50 Crl:CD1 (ICR) mice of each sex received fenpicoxamid (purity 79.4%) in the diet at a concentration of 0, 50, 300 or 1500 ppm (males) or 0, 50, 300 or 3000 ppm (females) (corrected for test substance purity; equal to 0, 5.3, 32 and 156 mg/kg bw per day for males and 0, 6.8, 40 and 388 mg/kg bw per day for females, respectively). Animals were monitored daily for mortality and moribundity and biweekly for clinical signs of toxicity. Detailed clinical observations were performed on 10 animals of each sex per group monthly for the first 13 months of treatment and at months 15 and 18. Body weight, body weight gain and feed consumption were measured weekly for the first 13 months of treatment and monthly thereafter. Ophthalmological examinations were performed pre-exposure and prior to scheduled necropsy. White blood cell counts were analysed from samples taken from the pedal vein at 12 months and orbital sinus at 18 months,

and toxicokinetics was analysed in urine and whole blood. Gross examinations were performed and organs were weighed in all animals, and histopathological examination was performed on animals from the control and high-dose groups and all animals killed in extremis or found dead.

There were no effects on mortality, clinical signs of toxicity, body weight, feed consumption or white blood cell counts. There were no gross changes to the liver; however, liver weights were increased in males in all treated groups and in females at 3000 ppm. Based on the lack of histopathological changes and dose–response relationship, the increased liver weights were considered adverse only at 1500/3000 ppm in both sexes. There was an increase in calculi in the lumen of gall bladders in males and females at 300 ppm and above, indicating a possible alteration of liver metabolism. Hypertrophy with altered tinctorial properties was increased in males at 300 ppm and above and in females at 3000 ppm. Multifocal single-cell necrosis was increased in males in all treated groups and in females at 3000 ppm; however, the changes were considered treatment related and adverse only at the high dose in both sexes. Hepatocyte vacuolization consistent with fatty change was increased at 1500 ppm in males in the midzonal and centrilobular regions of the liver, whereas in females the vacuolization was multifocal and involved individual cells at 3000 ppm. There was an increase in intrahepatocellular erythrocytes in males at 1500 ppm. In males, hepatocellular adenomas were increased, although within the historical control range, at 300 ppm, and adenomas and carcinomas were increased at 1500 ppm (Table 11).

Table 11. Effects in the 18-month oral toxicity study in mice

	Males				**Females**			
	0 ppm	**50 ppm**	**300 ppm**	**1 500 ppm**	**0 ppm**	**50 ppm**	**300 ppm**	**3 000 ppm**
Organ weights								
Liver								
Absolute (g)	2.44 ± 0.43	3.16 ± 3.12	2.58 ± 0.56	2.86 ± 0.63*	2.22 ± 0.58	1.94 ± 0.29	2.30 ± 1.50	2.51 ± 0.62*****
Relative (g/100 g)	5.03 ± 0.97	6.51 ± 4.99	5.56 ± 1.28	5.95 ± 1.23	5.25 ± 1.40	4.85 ± 0.61	5.36 ± 3.08	6.034 ± 1.78*
Histopathology								
Adrenal (no. examined)	50	50	50	50	50	50	50	50
Hypertrophy; zona fasciculata; unilateral; focal; slight	3	1	0	0	0	0	0	0
Hypertrophy; zona fasciculata; unilateral; diffuse; slight	1	0	0	0	0	0	0	0
Gall bladder (no. examined)	46	45	38	47	49	50	48	49
Calculi, lumen	4	2	10	14*	2	2	6	10*
Liver (no. examined)	50	50	50	50	50	50	50	50
Hypertrophy, with altered tinctorial properties, hepatocyte, centrilobular/midzonal	5	4	21*	37*	2	5	5	32*
- very slight	4	4	20*	15*	2	3	5	11*
- slight	1	0	1	20*	0	2	0	21*

	Males				Females			
	0 ppm	**50 ppm**	**300 ppm**	**1 500 ppm**	**0 ppm**	**50 ppm**	**300 ppm**	**3 000 ppm**
- moderate	0	0	0	2	0	0	0	0
Necrosis; hepatocyte; individual cells; multifocal	1	4	3	12*	0	1	0	2
- very slight	1	4	3	11*	0	1	0	2
- slight	0	0	0	1	0	0	0	0
Vacuolization; consistent with fatty change; hepatocyte; centrilobular/midzonal	5	3	4	15*	0	0	1	2
- very slight	1	3	2	9*	0	0	1	2
- slight	3	0	2	5	0	0	0	0
- moderate	1	0	0	1	0	0	0	0
Vacuolization; consistent with fatty change; hepatocyte; individual cells; multifocal; very slight	0	0	0	1	1	0	0	10*
Intrahepatocellular erythrocytes; multifocal	1	2	1	11*	0	0	0	0
- very slight	1	2	1	8*	0	0	0	0
- slight	0	0	0	3	0	0	0	0
Tumour incidences								
Adrenal glands								
Adenoma; unilateral; subcapsular; benign; primary	0	1	1	3	0	0	0	0
Liver								
Adenoma; hepatocyte; benign; primary	4	2	7	8	1	0	1	0
Adenoma; two; hepatocyte; benign; primary	0	0	3	2	0	0	0	0
Adenoma; three; hepatocyte; benign; primary	0	1	1	0	0	0	0	0
Adenoma; five; hepatocyte; benign; primary	0	0	0	1	0	0	0	0
Total no. of animals with one or more adenomas; hepatocyte; benign;	4	3	11	11	1	0	1	1

	Males				Females			
	0 ppm	**50 ppm**	**300 ppm**	**1 500 ppm**	**0 ppm**	**50 ppm**	**300 ppm**	**3 000 ppm**
primary								
Historical controls			*4–12*					
Carcinoma; hepatocyte; malignant without metastasis; primary	1	3	0	4	0	0	0	0
Historical controls			*0–2*					
Total no. of animals with one or more adenomas and/or carcinomas; hepatocyte; benign; primary	5	6	11	13	1	0	1	0
Historical controls			*4–13*					

ppm: parts per million
Source: Thomas, Murray & McCoy (2013)

The NOAEL for toxicity was 50 ppm (equal to 5.3 mg/kg bw per day), based on altered liver metabolism and increased hepatocellular hypertrophy in males at 300 ppm (equal to 32 mg/kg bw per day). The NOAEL for carcinogenicity was 50 ppm (equal to 5.3 mg/kg bw per day), based on an equivocal increase in the incidence of liver adenomas in males at 300 ppm (equal to 32 mg/kg bw per day) (Thomas, Murray & McCoy, 2013).

Rats

In an oral 2-year toxicity and carcinogenicity study, groups of 50 F344/DuCrl rats of each sex received fenpicoxamid (purity 79.4%) in the diet at a targeted dose of 0, 100, 300 or 1000 mg/kg bw per day (equivalent to concentrations of 0, 3000, 10 000 and 30 000 ppm, respectively, corrected for test substance purity; achieved doses of 0, 101, 303 and 1009 mg/kg bw per day for males and 0, 101, 302 and 1009 mg/kg bw per day for females, respectively). An additional 10 rats of each sex per group served as a 12-month satellite group at the same doses. Animals were monitored daily for mortality and moribundity and biweekly for clinical signs of toxicity. Detailed clinical observations were performed on 10 animals of each sex per group monthly for the first 12 months of treatment and at months 15, 18, 21 and 24. Body weight, body weight gain and feed consumption were measured weekly for the first 13 months of treatment and monthly thereafter. Ophthalmological examinations were performed pre-exposure and prior to scheduled necropsy. Haematology, clinical chemistry and urine analysis parameters were examined in samples taken from 10 animals of each sex per dose at 3, 6, 12, 18 and 24 months, and toxicokinetics was analysed in urine and whole blood. Thyroid hormone and blood iodine analyses were performed on retained sera samples from the 3- and 12-month samples and the 24-month sample, respectively. Gross examinations were performed and organs were weighed in all animals, and histopathological examination was performed on animals from the control and high-dose groups and on all animals killed in extremis or found dead.

There were no effects on mortality, clinical signs of toxicity, feed consumption, haematological or coagulation parameters or gross pathology.

Final body weights were decreased in 30 000 ppm females only (Table 12).

Table 12. Effects in the 2-year oral toxicity and carcinogenicity study in rats

	Males				Females			
	0 ppm	**3 000 ppm**	**10 000 ppm**	**30 000 ppm**	**0 ppm**	**3 000 ppm**	**10 000 ppm**	**30 000 ppm**
Body weight								
Initial (g)	149.4 ± 12.7	149.2 ± 13.0	148.1 ± 13.1	148.1 ± 11.9	101.8 ± 5.8	100.5 ± 5.2	99.8 ± 5.2	99.2* ± 5.1
Final (g)	419.7 ± 31.1	424.3 ± 25.1	412.7 ± 29.9	411.7 ± 23.1	280.6 ± 21.0	270.7 ± 18.8	271.5 ± 20.2	263.2* ± 15.9 (↓ 6%)
Body weight gain (g) (% of controls)								
Week 1	32.5 (21.8%)	31.1 (20.8%)	31.1 (21%)	30.8 (20.8%)	17.8 (17.4%)	17.6 (17.5%)	17.5 (17.5%)	17.8 (17.9%)
Weeks 1–13	178.8 (119.7%)	176.5 (118.3%)	179.3 (121%)	179 (120.8%)	88.2 (86.6%)	83.6 (83.2%)	83.3 (84.1%)	80.7 (81.4%)
Weeks 13–26	231.1 (154.7%)	227.5 (152.5%)	232.3 (156.8%)	228.7 (154.4%)	103.5 (101.7%)	98.2 (97.7%)	100.8 (101%)	95.3 (96.1%)
Weeks 26–52	282.6 (189.2%)	279.7 (187.5%)	285.1 (192.5%)	277.1 (187.1%)	116.8 (114.7%)	110.9 (110.3%)	112.6 (112.8%)	110.9 (111.8%)
Weeks 52–75	300.6 (201.2%)	298.3 (200%)	302.3 (204.1%)	290.1 (195.8%)	152.6 (150%)	144.2 (143.5%)	146.3 (146.6%)	140.9 (142%)
Overall weeks −1 to 104	270	275.1	264.6	263.6	178.8	170.2	171.7	164
Blood thyroid hormone levels (% change)								
3 months (no. examined)	9	10	7	10	9	10	9	10
T_3 (ng/dL)	110 ± 9.6	109 ± 10.7 (↓ 1.2%)	105 ± 18.4 (↓ 5.0%)	101 ± 17.4 (↓ 8.0%)	116 ± 16.9	105 ± 23.2 (↓ 9.5%)	103 ± 15.3 (↓ 11.1%)	95 ± 16.9 (↓ 17.8%)
T_4 (µg/dL)	7.3 ± 1.0	6.3 ± 1.3 (↓ 13.3%)	6.0 ± 1.4 (↓ 17.9%)	6.1 ± 1.4 (↓ 16.6%)	3.6 ± 1.2	4.0 ± 1.2 (↑ 10.0%)	3.2 ± 1.1 (↓ 12.2%)	3.3 ± 0.9 (↓ 9.7%)

	Males				Females			
	0 ppm	**3 000 ppm**	**10 000 ppm**	**30 000 ppm**	**0 ppm**	**3 000 ppm**	**10 000 ppm**	**30 000 ppm**
12 months (no. examined)	10	10	10	10	10	10	10	10
T_3 (ng/dL)	102 ± 10.7	90 ± 14.9 (↓ 12.4%)	99 ± 10.7 (↓ 3.5%)	88 ± 10.1* (↓ 13.8%)	128 ± 34.7[a] 118 ± 14.4[b]	115 ± 17.1 (↓ 10.2%) (↓ 2.5%)	113 ± 16.0 (↓ 12.2%) (↓ 4.2%)	109 ± 11.3 (↓ 15.4%) (↓ 7.6%)
T_4 (µg/dL)	5.5 ± 1.4	5.4 ± 1.3 (↓ 2.5%)	4.5 ± 1.2 (↓ 17.8%)	4.5 ± 0.5 (↓ 18.3%)	2.8 ± 0.7	3.2 ± 1.4 (↑ 11.6%)	3 ± 0.7 (↑ 6.0%)	2.5 ± 0.7 (↓ 11.6%)
TSH (ng/mL)	2.3 ± 0.4	2.2 ± 0.9 (↓ 5.6%)	2.6 ± 0.9 (↑ 10.7%)	2.4 ± 0.6 (↑ 3.4%)	3.1 ± 1.1	2.1 ± 0.6 (↓ 31.2%)	2.2 ± 0.6 (↓ 29.6%)	2.1 ± 0.3 (↓ 31.8%)
24 months (no. examined)	20	20	20	20	20	20	20	20
T_3 (ng/dL)	83 ± 9.5	86 ± 14.7 (↑ 3.1%)	83 ± 16.5 (↓ 0.4%)	81 ± 7.5 (↓ 3.5%)	97 ± 11	105 ± 12.9 (↑ 8.7%)	99 ± 15.0 (↑ 2.6%)	105 ± 12.8 (↑ 8.2%)
T_4 (µg/dL)	3.6 ± 0.8	3.3 ± 0.8 (↓ 7.3%)	3.8 ± 0.8 (↑ 10.3%)	3.3 ± 0.5 (↓ 7.8%)	2.7 ± 0.4	2.7 ± 0.4 (↑ 0.4%)	2.4 ± 0.5 (↓ 10.7%)	2.2 ± 0.5* (↓ 18.8%)
TSH (ng/mL)	1.7 ± 0.5	1.9 ± 1.2 (↑ 10.3%)	1.8 ± 0.5 (↑ 5.7%)	2.1 ± 0.8 (↑ 19.5%)	1.8 ± 0.5	1.6 ± 0.3 (↓ 7.9%)	1.8 ± 0.3 (↑ 4.0%)	1.9 ± 0.4 (↑ 5.6%)
Whole blood iodide (ng/g)								
Organic iodide, calculated from T_3 and T_4[c]								
3 months	46 ± 7	42 ± 8	40 ± 9	40 ± 9	24 ± 8	27 ± 8	21 ± 7	22 ± 6
12 months	37 ± 9	36 ± 8	30 ± 8	30 ± 3	19 ± 4	21 ± 9	20 ± 5	17 ± 4
24 months	24 ± 6	22 ± 5	25 ± 5	22 ± 4	18 ± 3	19 ± 3	17 ± 3	15 ± 3
Measured total iodide (% change)								
24 months	107 ± 40	115 ± 52 (↑ 7%)	134 ± 41 (↑ 25%)	215 ± 80* (↑ 100%)	84 ± 55	77 ± 40 (↓ 8.3%)	104 ± 51 (↑ 23.8%)	161 ± 91* (↑ 91.6%)

	Males				Females			
	0 ppm	**3 000 ppm**	**10 000 ppm**	**30 000 ppm**	**0 ppm**	**3 000 ppm**	**10 000 ppm**	**30 000 ppm**
95% CI	± 25	± 32	± 25	± 50	± 34	± 25	± 31	± 57
Range	82–132	83–147	109–159	165–265	50–118	52–102	73–135	104–218
Adjusted mean[d]	3	11	30	111	7	0	27	84
Maximum calculated iodide intake due to fenpicoxamid in µg/day (µg/kg bw per day)								
24 months[e]	0	2.4 (5.8)	7.3 (17.4)	24.2 (58)	0	1.6 (5.8)	4.7 (17.4)	15.7 (58)
Urine analysis: pH (% of animals with urinary pH of 7.5 and higher)								
3 months	7.4 (20%)	7.35 (0%)	7.9 (60%)	8.1 (90%)	7.4 (20%)	7.55 (30%)	7.65 (50%)	8.15 (80%)
6 months	7.7 (40%)	7.9 (60%)	8.25 (100%)	8.4 (100%)	7.5 (30%)	8.25 (90%)	8.1 (70%)	8.35 (90%)
12 months	8.05 (70%)	7.75 (40%)	8.5 (90%)	8.5 (100%)	8.1 (80%)	8.2 (60%)	8.0 (60%)	8.55 (100%)
18 months	8.05 (80%)	7.8 (50%)	7.8 (60%)	8.25 (90%)	7.8 (50%)	7.4 (20%)	7.8 (30%)	8.1 (80%)
24 months	7.3 (20%)	7.15 (0%)	7.45 (10%)	7.8 (50%)	7.2 (0%)	7.2 (0%)	7.25 (0%)	7.45 (20%)
Organ weights (% change)								
Absolute kidney (g)								
12 months	2.357 ± 0.176	2.361 ± 0.136	2.390 ± 0.072 (↑ 1%)	2.525 ± 0.122* (↑ 7%)	1.384 ± 0.067	1.359 ± 0.084	1.414 ± 0.076 (↑ 2%)	1.443 ± 0.094 (↑ 4%)
24 months	2.594 ± 0.21	2.705 ± 0.20 (↑ 4%)	2.712 ± 0.24 (↑ 5%)	2.787 ± 0.21* (↑ 7%)	1.735 ± 0.11	1.757 ± 0.16 (↑ 1%)	1.793 ± 0.14 (↑ 3%)	1.830 ± 0.11* (↑ 5%)
Relative kidney (g/100 g)								
12 months	0.571 ± 0.029	0.578 ± 0.020	0.584 ± 0.025	0.605 ± 0.021*	0.689 ± 0.035	0.692 ± 0.026	0.716 ± 0.021	0.740 ± 0.036*

	Males				Females			
	0 ppm	**3 000 ppm**	**10 000 ppm**	**30 000 ppm**	**0 ppm**	**3 000 ppm**	**10 000 ppm**	**30 000 ppm**
			(↑ 2%)	(↑ 6%)			(↑ 4%)	(↑ 7%)
24 months	0.657 ± 0.09	0.681 ± 0.06 (↑ 4%)	0.705 ± 0.07* (↑ 7%)	0.722 ± 0.06* (↑ 10%)	0.663 ± 0.056	0.690 ± 0.062 (↑ 4%)	0.700 ± 0.053* (↑ 6%)	0.740 ± 0.049* (↑ 12%)
Absolute thyroid (mg)								
12 months	17.3 ± 2.9	17.6 ± 2.2	17.4 ± 1.8	19.4 ± 0.8* (↑ 12%)	11.3 ± 0.7	11.2 ± 1.1	11.7 ± 1.2 (↑ 4%)	13.5 ± 0.7* (↑ 16%)
24 months	22.0 ± 4.4	25.4 ± 10.6 (↑ 15%)	24.1 ± 3.6[$] (↑ 10%)	26.9 ± 4.6[$] (↑ 22%)	17.8 ± 5.9	18.2 ± 6.8 (↑ 2%)	19.4 ± 3.7[$] (↑ 11%)	20.9 ± 3.4[$] (↑ 17%)
Relative thyroid (mg/100 g)								
12 months	4.2 ± 0.4	4.3 ± 0.4	4.2 ± 0.3	4.7 ± 0.2* (↑ 12%)	5.6 ± 0.4	5.7 ± 0.6	5.9 ± 0.6 (↑ 5%)	6.9 ± 0.4* (↑ 23%)
24 months	5.6 ± 1.2	6.2 ± 2.7 (↑ 11%)	6.3 ± 0.9[$] (↑ 13%)	6.9 ± 1.1[$] (↑ 23%)	6.8 ± 2.0	7.1 ± 2.5 (↑ 4%)	7.6 ± 1.9 (↑ 12%)	8.4 ± 1.5* (↑ 23%)
Histopathology								
12 months								
Thyroid (no. examined)	10	10	10	10	10	10	10	10
Dilatation, increased, follicle, multifocal	1	5	6	2	3	5	2	1
- very slight	0	2	1	0	0	2	0	1
- slight	1	3	5	2	3	3	2	0
Dilatation, increased, follicle, diffuse	0	4	4	9	0	5	8	9
Aggregates of macrophages/histiocytes, multifocal	3	5	5	9	1	7	6	9

	Males				Females			
	0 ppm	**3 000 ppm**	**10 000 ppm**	**30 000 ppm**	**0 ppm**	**3 000 ppm**	**10 000 ppm**	**30 000 ppm**
Kidney (no. examined)	10	0	0	10	10	0	0	10
Chronic progressive glomerulonephropathy	10	0	0	10	4	0	0	2
- very slight	10	0	0	9	4	0	0	2
- slight	0	0	0	1	0	0	0	0
24 months								
Thyroid (no. examined; % change)	49	49	50	50	50	50	50	50
Dilatation, increased, follicle, multifocal – slight	9	35* (↑ 74%)	25* (↑ 64%)	2 (↓ 77.8%)	21	32* (↑ 34%)	40* (↑ 47.5%)	17 (↓ 19%)
Dilatation, increased, follicle, diffuse – slight	5	5	24* (↑ 79%)	48* (↑ 90%)	3	5 (↑ 40%)	6 (↑ 50%)	32* (↑ 91%)
Dilatation, increased, follicle, multifocal or diffuse – slight	14	40* (↑ 65%)	49* (↑ 71%)	50* (↑ 72%)	24	37* (↑ 35%)	46* (↑ 48%)	49* (↑ 51%)
Aggregates of macrophages/ histiocytes, focal – very slight	2	6	4	0	12	8	6	5
Aggregates of macrophages/ histiocytes, multifocal – very slight	25	31 (↑ 19%)	37* (↑ 32%)	46* (↑ 46%)	11	24* (↑ 54%)	25* (↑ 56%)	37* (↑ 70%)
Aggregates of macrophages/ histiocytes, multifocal – slight	0	0	0	0	1	0	0	0
Aggregates of macrophages/ histiocytes, focal or multifocal – very slight or slight	27	37 (↑ 27%)	41* (↑ 34%)	46* (↑ 41%)	24	32 (↑ 25%)	31 (↑ 23%)	42* (↑ 43%)
Kidneys (no. examined)	50	50	50	50	50	50	50	50
Chronic progressive glomerulonephropathy								

	Males				Females			
	0 ppm	**3 000 ppm**	**10 000 ppm**	**30 000 ppm**	**0 ppm**	**3 000 ppm**	**10 000 ppm**	**30 000 ppm**
- very slight	37	36	29	22*	42	13	7	37
- slight	8	9	17 (↑ 53%)	19* (↑ 58%)	2	0	2	2
- moderate	4	3	3	8 (↑ 50%)	0	0	0	0
- severe	1	2	1	1	0	0	0	0
Ovaries (no. examined)	–	–	–	–	50	14	11	49
Adenocarcinoma; malignant with metastasis; primary	–	–	–	–	0	0	0	2
Uterus (no. examined)	–	–	–	–	50	26	20	49
Adenocarcinoma; malignant with metastasis; primary	–	–	–	–	1	0	0	1
Adenocarcinoma; malignant without metastasis; primary	–	–	–	–	0	0	0	3

bw: body weight; CI: confidence interval; ppm: parts per million; T_3: triiodothyronine; T_4: thyroxine; TSH: thyroid stimulating hormone; *: $P < 0.05$ (Dunnett's test); $: $P < 0.05$ (Wilcoxon's test)

[a] Statistical outlier = 219.26 ng/dL.

[b] With statistical outlier removed.

[c] Calculated by the reviewer from the sum of T_3 and T_4 levels assuming the density of blood is 1 g/mL.

[d] Based on the intercept value in ng/g for the male (iodine = 0.1096 × dose + 104.39, R^2 = 0.9975) and female (iodine = 0.0833 × dose + 77.35, R^2 = 0.9719) linear regressions against treatment dose.

[e] Calculations were based on an iodide impurity level of 58 ppm in the test substance, 100, 300 and 1000 mg/kg bw per day of test material intake, and body weights of 0.417 kg for males and 0.272 kg for females.

Source: Stebbins et al. (2014)

There was an increase in urine alkalinization at 6 months in males and females at 3000 ppm, at 3 and 12 months in males at 10 000 ppm and at 18 and 24 months in males and females at 30 000 ppm. The changes were considered adverse at 10 000 ppm in the presence of an increase in relative kidney weights at 24 months and an increased incidence of chronic progressive glomerulonephropathy; however, the treatment-related nature of the changes is unknown, as this is a common lesion of the ageing rat.

Triiodothyronine (T_3) was decreased at increasing time points in males and females starting at 3000 ppm, and thyroxine (T_4) was decreased in males at 3000 ppm and above and in females at 10 000 ppm and above. Thyroid stimulating hormone (TSH), however, was increased only at 10 000 ppm and above in males at 12 and 24 months and in females at 24 months (Table 12). The effects on T_3 and T_4 were considered adverse only in the presence of effects on TSH. Thyroid weights were increased at 3000 ppm and above. Histopathologically, there is an increase in multifocal to diffuse dilatation of follicles and aggregates of macrophages/histiocytes at 3000 ppm and above in both sexes. According to the study authors, the thyroid toxicity is a result of iodide impurities in the active ingredient, as evidenced by the increased blood iodide level in males at 3000 ppm and in females at 10 000 ppm (Table 12). However, there was insufficient evidence to support this proposed mode of action. The effects on the thyroid hormones were limited, and the additional 6 µg/kg bw per day iodide over the approximately 15 µg/kg bw per day already present in the diet of the low-dose animals would not be expected to have as large an effect as is seen in this study. In addition, the finding of aggregates of macrophages/histiocytes at the lowest dose tested is sufficiently rare as to cause concern.

Although not statistically significant, ovarian tumours in the rat are a very rare tumour type, and the increase at 30 000 ppm would be considered treatment related.

A NOAEL for toxicity was not identified, based on increased thyroid weight and thyroid histopathology changes and increased blood iodide at 3000 ppm (equal to 101 mg/kg bw per day), the lowest dose tested.

The NOAEL for carcinogenicity was 10 000 ppm (equal to 302 mg/kg bw per day), based on an increased incidence of ovarian adenocarcinomas in females at 30 000 ppm (equal to 1009 mg/kg bw per day) (Stebbins et al., 2014).

2.4 Genotoxicity

(a) In vitro studies

A range of in vitro studies of the genotoxicity of fenpicoxamid was conducted to assess its potential for inducing chromosomal aberration, gene mutation and reverse mutation (summarized in Table 13). There was one positive result, the chromosomal aberration assay in rat lymphocytes. There was a significant increase in aberrations (primarily chromatid breaks and exchanges) in the absence of S9 (the 9000 × *g* supernatant fraction from rat liver homogenate) after 4 hours at 100 µg/mL compared with both current and historical controls in both experiments, and there was a positive linear trend in aberrations in the presence of S9 fraction in the second experiment. There were no effects on polyploidy after 24 hours of exposure.

(b) In vivo studies

Unscheduled DNA synthesis and micronucleus assays were conducted to assess the potential of fenpicoxamid to damage DNA and impede repair in vivo (summarized in Table 13). There was no evidence of genotoxicity.

As there was no evidence of genotoxic effects in the in vivo studies, the concern from the in vitro chromosomal aberration study is lessened. Overall, there was no evidence for genotoxicity or mutagenicity in the presence or absence of metabolic activation.

Table 13. Genotoxicity studies with fenpicoxamid

End-point	Test object	Concentration	Purity (%)	Results	Reference
In vitro					
Reverse mutation	*Salmonella typhimurium* and *Escherichia coli*	1.5, 5.0, 15, 50, 150, 500, 1 500 or 5 000 µg/plate ± S9	78.0	Negative	Dakoulas & Divi (2010)
Chromosomal aberration	Rat lymphocytes	25, 50 or 100 µg/mL ± S9	78.0	Positive	Schisler (2011a)
Mammalian forward mutation	Chinese hamster ovary cells (CHO/HPRT)	6.25–100 µg/mL ± S9	78.0	Negative	Schisler (2011b)
In vivo					
Mouse micronucleus	CD-1 mouse bone marrow, males	0, 500, 1 000 or 2 000 mg/kg bw	78.0	Negative	Schisler (2011c)
Unscheduled DNA synthesis	Hsd:ICR (CD-1) mouse liver cells, males	2 000 mg/kg bw	79.4	Negative	Pant (2014)

bw: body weight; CHO/HPRT: Chinese hamster ovary hypoxanthine–guanine phosphoribosyl transferase; S9: 9000 × *g* supernatant fraction from liver homogenate from phenobarbital- and 5,6-benzoflavone-treated rats

2.5 Reproductive and developmental toxicity

(a) Multigeneration studies

In a range-finding one-generation reproductive toxicity study, groups of four Crl:CD(SD) rats of each sex received fenpicoxamid (purity 78.0%) at a dietary concentration of 0, 5769, 11 538 or 17 308 ppm (0, 4500, 9000 and 13 500 ppm, respectively, corrected for test substance purity; equal to 0, 370, 748 and 1113 mg/kg bw per day for males and 0, 350, 697 and 1049 mg/kg bw per day for females, respectively). Animals were monitored daily for mortality and moribundity and weekly for clinical signs of toxicity. Body weight and body weight gain were measured weekly in males and weekly during the prebreeding phase and on gestation days (GDs) 0, 7, 14 and 20 and lactation days (LDs) 0, 1, 4, 7, 14 and 21 in females. Feed consumption was measured weekly during prebreeding but was not measured during breeding due to co-housing. Breeding commenced 2 weeks after the start of treatment, litters were recorded as soon as possible following delivery and litters were culled on LD 4. Toxicokinetics was analysed in whole blood of males and females, milk of lactating females and whole blood of culled F_1 pups. Gross examinations were performed and organs were weighed in all adults, and the uteri of all females were stained for examination. Pups were subjected to a gross external examination. Histopathological examination was performed on all adults from the control and high-dose groups.

In the parental animals, there were no effects on mortality, clinical signs of toxicity, body weight, body weight gain or feed consumption. At 4500 ppm, liver weights were slightly increased in males. At 13 500 ppm, there were histopathological changes in the liver of both males and females, consisting of multifocal necrosis with accompanying inflammation and vacuolization consistent with fatty change in males and periportal vacuolization consistent with fatty change in females.

There were no effects on reproductive parameters.

In the offspring, there were decreases in pup weight compared with controls starting at 4500 ppm (Rasoulpour et al., 2012a).

In a two-generation reproductive toxicity study, groups of 25 Crl:CD(SD) rats of each sex received fenpicoxamid (purity 79.4%) at a dietary concentration of 0, 1729, 5052 or 16 614 ppm

(equal to 0, 107, 322 and 1066 mg/kg bw per day, respectively, corrected for purity of test substance) for males and 0, 1362, 4005 or 13 383 ppm (equal to 0, 105, 315 and 1052 mg/kg bw per day, respectively, corrected for purity of test substance) for females. Animals were monitored twice daily for mortality and moribundity and weekly for clinical signs of toxicity. Body weight and body weight gain were measured weekly in males and weekly during the prebreeding phase and on GDs 0, 7, 14 and 20 and LDs 0, 1, 4, 7, 14 and 21 in females. Feed consumption was measured weekly during prebreeding but was not measured during breeding due to co-housing. Breeding commenced 2 weeks after the start of treatment, litters were recorded as soon as possible following delivery and litters were culled on LD 4. F_1 litters were weaned on postnatal day (PND) 21, and one male and one female from each litter were randomly selected as F_1 parental animals to produce the second (F_2) generation. Selected F_1 animals were monitored daily for onset of puberty. Gross examinations were performed and organs were weighed in all adults, and the uteri of all females were stained for examination. Histopathological examination was performed on all adults from the control and high-dose groups. Three pups of each sex per litter were subjected to a gross necropsy after random selection on PND 22, and one of the three pups of each sex per litter was examined grossly for select organ weights.

In parental animals, there were no effects on mortality, body weight, feed consumption, clinical signs of toxicity, gross pathology, histopathology or organ weights.

There were no effects on reproductive parameters.

In offspring, there were no effects on litter parameters, pup body weights, gross necropsy or organ weights.

The NOAEL for parental toxicity was 13 383 ppm (equal to 1052 mg/kg bw per day), the highest dose tested.

The NOAEL for reproductive toxicity was 13 383 ppm (equal to 1052 mg/kg bw per day), the highest dose tested.

The NOAEL for offspring toxicity was 13 383 ppm (equal to 1052 mg/kg bw per day), the highest dose tested (Ellis-Hutchings et al., 2013).

(b) Developmental toxicity

Rats

In a preliminary developmental toxicity study, groups of six premated female Crl:CD(SD) rats were given fenpicoxamid (purity 78.0%) at a concentration of 0, 4500, 9000 or 13 500 ppm (corrected for test substance purity; equal to 0, 322, 639 and 977 mg/kg bw per day, respectively) in the diet from GD 6 to GD 21. Animals were monitored twice daily for mortality and moribundity and daily for clinical signs of toxicity. Body weight and body weight gain were measured daily during treatment (GDs 6–21), and feed consumption was measured every 3 days from GD 6 to GD 21. A blood sample was taken for toxicokinetics at necropsy, and all surviving animals were subjected to gross necropsy and uterine staining. Fetuses were examined for external malformations.

In dams, there were no effects on mortality, clinical signs of toxicity, body weight, body weight gain, feed consumption, caesarean section parameters or gross necropsy.

In fetuses, there were no developmental effects noted (Rasoulpour et al., 2012b).

In a developmental toxicity study, groups of 24 premated female Crl:CD(SD) rats were given fenpicoxamid (purity 79.4%) at a concentration of 0, 1350, 4050 or 13 500 ppm (corrected for purity of the test substance; equal to 0, 103, 311 and 1036 mg/kg bw per day, respectively) in the diet from GD 6 to GD 21. Animals were monitored twice daily for mortality and moribundity and daily for clinical signs of toxicity. Body weight and body weight gain were measured daily during treatment (GDs 6–21), and feed consumption was measured every 3 days from GD 6 to GD 21. A blood sample

was taken for toxicokinetics at necropsy, and all surviving animals were subjected to gross necropsy and uterine staining. All fetuses were examined for body weight, sex and external malformations. Half of each group was examined for visceral malformations, and the remaining half was stained and examined for skeletal malformations.

In dams, there were no effects on mortality, body weight or feed consumption, clinical signs of toxicity, caesarean section parameters or gross necropsy findings.

In fetuses, there were no effects on viability, sex ratios or body weights or treatment-related effects on malformations or variations.

The NOAEL for maternal toxicity was 13 500 ppm (equal to 1036 mg/kg bw per day), the highest dose tested.

The NOAEL for embryo and fetal toxicity was 13 500 ppm (equal to 1036 mg/kg bw per day), the highest dose tested (Rasoulpour, Marshall & McCoy, 2012).

Rabbits

In a preliminary developmental toxicity study, groups of five female premated New Zealand white rabbits were given fenpicoxamid (purity 79.4%) at a concentration of 0, 12 250 or 24 500 ppm (corrected for test substance purity; equal to 0, 460 and 630 mg/kg bw per day, respectively) in the diet from GD 7 to GD 28. Animals were monitored twice daily for mortality and moribundity and daily for clinical signs of toxicity. Body weight and feed consumption were measured daily during treatment (GDs 7–28), and statistical analyses were conducted on GDs 0, 7, 10, 13, 16, 20, 24 and 28. A blood sample was taken for toxicokinetics at GD 27, and all surviving animals were subjected to gross necropsy and uterine staining. Fetuses were weighed; however, no further examinations were performed.

The 24 500 ppm group was killed in extremis due to body weight loss, decreased feed consumption and decreased faecal output on GD 14. There were no treatment-related effects in the 12 250 ppm group (Rasoulpour et al., 2012c).

In a developmental toxicity study, groups of 25 female premated New Zealand white rabbits were given fenpicoxamid (purity 79.4%) at a dietary concentration of 0, 1889, 6297 or 18 891 ppm (0, 1500, 5000 and 15 000 ppm, respectively, corrected for test substance purity; equal to 0, 52.8, 177 and 495 mg/kg bw per day, respectively) from GD 7 to GD 28. Animals were monitored twice daily for mortality and moribundity and daily for clinical signs of toxicity. Body weight and feed consumption were measured daily during treatment (GDs 7–8), and statistical analyses were conducted on GDs 0, 7, 10, 13, 16, 20, 24 and 28. A blood sample was taken for toxicokinetics on GD 27, and all surviving animals were subjected to gross necropsy and uterine staining. All fetuses were examined for body weight, sex, and external and visceral malformations. Half of each group was stained and examined for craniofacial malformations, and all fetuses were stained and examined for skeletal malformations.

In the dams at 1500 ppm, there were decreases in body weight gain and feed consumption that were not considered adverse, as there were no effects on body weight. At 5000 ppm and above, animals exhibited decreased feed consumption, decreased body weight gain and decreased faecal output. At 15 000 ppm, there was body weight loss and decreased feed consumption.

In fetuses, there were no treatment-related effects on developmental parameters.

The NOAEL for maternal toxicity was 1500 ppm (equal to 52.8 mg/kg bw per day), based on decreased body weight gain, feed consumption and faecal output at 5000 ppm (equal to 177 mg/kg bw per day).

The NOAEL for embryo and fetal toxicity was 15 000 ppm (equal to 495 mg/kg bw per day), the highest dose tested (Ellis-Hutchings, Bell & McCoy, 2013).

2.6 Special studies

(a) Neurotoxicity

No studies were submitted.

(b) Immunotoxicity

No studies were submitted.

(c) Studies on metabolites

The acute toxicity and genotoxicity of metabolite X642188 are summarized in Tables 14 and 15, respectively.

Table 14. Acute toxicity study on a metabolite of fenpicoxamid

Test substance	Species	Strain	Sex	Route	Purity (%)	Result	Reference
X642188	Rat	Wistar	Female	Oral	99	LD_{50} > 2 000 mg/kg bw	Dalal (2013)

bw: body weight; LD_{50}: median lethal dose

Table 15. Genotoxicity study on a metabolite of fenpicoxamid

Test substance	End-point	Test object	Concentration	Purity (%)	Results	Reference
In vitro						
X642188	Reverse mutation	*Salmonella typhimurium*	51.2, 128, 320, 800, 2 000 and 5 000 µg/plate ± S9	99	Negative	Patel (2012)

S9: 9000 × *g* supernatant fraction from rat liver homogenate

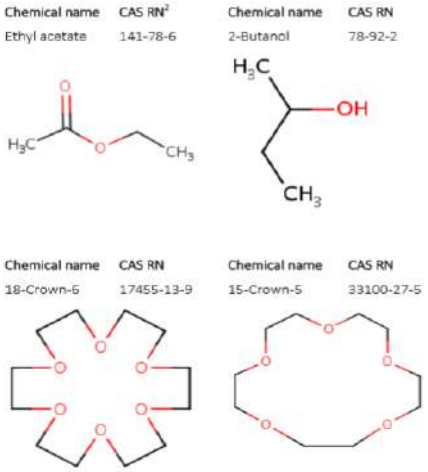
Of the metabolites identified as process hydrolysis degradates, X12335723, X12264475 and X12019520 were flagged for possible genotoxic effects. X12335723 and X12264475 were also embedded in the parent. As such, if weight of evidence suggests that the parent is non-genotoxic, the level of concern is also low for hydrolysis degradates. X12314005 was not seen as a metabolite in the ADME studies, but had no flags for genotoxicity. X12019520 is not a known metabolite in the rat and, due to its small size, is not considered covered by the alerts in the parent. Read-across data from an analogue, RN-3734-22-3, would lessen concern for genotoxicity in humans (Dow, date unknown).

Insufficient information was available to evaluate the toxicological relevance of the metabolites X12326349 (animal metabolite), X696872 (animal metabolite) and X12019520 (simulated processing product).

(d) Investigation of impurities

The purity of the fenpicoxamid used in the toxicity studies ranged between 78.0% and 84.2%. In addition to the iodine cited as an impurity in the 2-year rat oral toxicity study, four impurities were isolated from the test substance: ethyl acetate (CAS no. 141-78-6), 2-butanol (CAS no. 78-92-2), 18-crown-6 (CAS no. 17455-13-9) and 15-crown-5 (CAS no. 33100-27-5) (Fig. 4).

Fig. 4. Structures of impurities found in fenpicoxamid



Source: O'Connell & Hopkins (2017)

The sponsor commissioned a consulting group to perform a search on the names and CAS numbers of the four impurities using the bibra TRACE database, the TOXNET system of databases, e-ChemPortal, the European Chemicals Agency Information on Chemicals database, PubMed and the Registry of Toxic Effects of Chemical Substances.

Ethyl acetate did not induce micronuclei in the bone marrow of mice or hamsters. It caused a weak positive reaction in the induction of aberrations in Chinese hamster lung fibroblast cells without S9 fraction and induced sister chromatid exchanges (SCEs) in Chinese hamster ovary (CHO) cells in the presence of S9. It did not induce unscheduled DNA synthesis in human lymphocytes. Ames tests were negative in *S. typhimurium* strains; however, aneuploidy and other genotoxicity were induced in *Saccharomyces cerevisiae*.

2-Butanol induced clastogenicity in a disputed study, and the evidence of genotoxicity in mammals was weak. Otherwise, 2-butanol was negative in chromosomal aberration assays in CHO cells, Ames tests in *S. typhimurium* or *E. coli* and a gene conversion assay in *S. cerevisiae*.

18-Crown-6 was considered possibly to have anti-mutagenic or co-mutagenic properties due to the ionophoric characteristics of crown ethers and the possibility of altering the structure of membranes to allow for enhanced uptake of other substances. No relevant in vivo mammalian data were identified. 18-Crown-6 did not induce chromosomal aberrations in the rat liver or CHO AA8 cells or SCEs in Chinese hamster (V79) cells. It was negative in *S. typhimurium* and *E. coli* in the Ames assay and in the gene conversion assay in *S. cerevisiae*.

15-Crown-6 was considered possibly to have anti-mutagenic or co-mutagenic properties due to the ionophoric characteristics of crown ethers and the possibility of altering the structure of membranes to allow for enhanced uptake of other substances. No relevant in vivo mammalian data were identified. 15-Crown-6 did not induce chromosomal aberrations in CHO AA8 cells. It was negative in *S. typhimurium* in the Ames assay (O'Connell & Hopkins, 2017).

(e) Microbiological effects

The fungicide fenpicoxamid was evaluated at the 2018 JMPR to determine its impact on microbiota in the gastrointestinal tract. As no data were submitted by the sponsors, a literature search was performed using a number of search engines. These included BioOne (http://www.bioone.org/), Google (https://www.google.com/), Google Scholar (http://scholar.google.com/), PubMed (http://www.ncbi.nlm.nih.gov/pubmed), ScienceDirect (http://www.sciencedirect.com/) and Web of Science (https://apps.webofknowledge.com).

The search strategy used the input keywords of the fungicide chemical name (fenpicoxamid), chemical structure, antimicrobial mode of action, antimicrobial spectrum of activity, antimicrobial resistance, resistance mechanisms and genetics, microbiome, microbiota, gut microbiota, gut microbiome, gastrointestinal microbiota, gastrointestinal microbiome, etc., as well as the Boolean operators AND, OR and NOT.

The extensive search and review of the scientific literature did not find any reports on the effects of fenpicoxamid on the intestinal microbiome to include in the toxicological risk assessment.

3. Observations in humans

In reports on manufacturing plant personnel, no adverse health effects were noted (Dow, 2016).

No information on accidental or intentional poisoning in humans is available.

Comments

Biochemical aspects

In ADME studies conducted in rats using fenpicoxamid labelled with ^{14}C at the phenyl-UL and 2-pyridine positions, the absorption of fenpicoxamid was rapid (T_{max} 2–5 hours) but low (5–20%). Plasma $AUC_{0–168\ h}$ values ranged from 13 to 24 µg·h/g at the low dose (10 mg/kg bw) and from 73 to 74 µg·h/g at the high dose (300 mg/kg bw), indicating a lack of dose proportionality. Elimination was rapid (58–90% of the administered dose within 24 hours) and predominately via the faeces. Biliary excretion of radiolabel was higher than urinary excretion and accounted for only a small fraction of the faecal excretion. Absorbed fenpicoxamid was completely metabolized, with no parent found in the urine. A significant portion of radioactivity was found bound within the faeces (~56% at the single low dose and ~34% at the single high dose), which may account for the lack of absorption. However, following repeated exposure, the portion bound in the faeces was reduced to approximately 14%, suggesting saturation of the binding sites in faecal material (Hansen et al., 2013; Press & Reynolds, 2013).

Tissue distribution was measured at C_{max} and ½ C_{max} (2 and 6–12 hours post-dosing, respectively). At those time points, the highest concentrations of radioactivity were in the gastrointestinal tract, urinary bladder, liver and kidneys. One hundred and sixty-eight hours following dosing, concentrations of radioactivity in all tissues were at or below 0.01% of the administered dose (Hansen, Clark & Staley, 2012; Hansen et al., 2013).

The principal routes of metabolism of fenpicoxamid involved hydrolysis of various ester groups, as well as *O*-dealkylation of the hydroxymethoxy side-chain of the pyridine ring. The primary metabolites were X1236349 and X696872; however, X1236349 also occurs as an impurity (Hansen et al., 2013; Zhang et al., 2014).

Toxicokinetics was analysed in all the short- and long-term studies of toxicity referenced below under “Toxicological data”. Overall, there was a low internal exposure to fenpicoxamid, as evidenced by low levels of parent compound and major metabolites in the urine and blood samples; saturation of absorption led to small increases in internal dose, even with large increases in the administered dose. Therefore, a proportionate dose–response relationship would not be expected.

Toxicological data

In rats, fenpicoxamid had an acute oral median lethal dose (LD_{50}) greater than 2000 mg/kg bw, an acute dermal LD_{50} greater than 5000 mg/kg bw and an acute inhalation median lethal concentration (LC_{50}) greater than 0.53 mg/L (Durando, 2011a,b; Krieger & Garlinghouse, 2012).

Fenpicoxamid was non-irritating to the skin and minimally irritating to the eyes of rabbits (Durando, 2011c,d). It was not a dermal sensitizer in mice (Boverhof & Sosinski, 2012). Fenpicoxamid did not cause phototoxicity in vitro (Roth, 2015).

The main toxic effects of fenpicoxamid in short- and long-term studies were liver changes, including adenomas and carcinomas, in the mouse; liver and thyroid changes in the rat; and body weight effects and liver changes in the dog.

In a 90-day study, mice received a dietary concentration of fenpicoxamid of 0, 300, 1500, 3000 or 6000/9000 ppm (males, increased at day 57) or 6000 ppm (females) (equal to 0, 40, 192, 399 and 921 mg/kg bw per day for males and 0, 49, 303, 566 and 1107 mg/kg bw per day for females, respectively), with recovery groups of 0, 6000 (females) and 3000/6000 (males) ppm given untreated diet for 28 days. The NOAEL was 300 ppm (equal to 40 mg/kg bw per day), based on increased liver weights and hepatocellular hypertrophy in males and females, decreased serum triglycerides, hepatocyte fatty change and multifocal single-cell necrosis in males and decreased serum albumin in females at 1500 ppm (equal to 192 mg/kg bw per day) (Thomas, Murray & McCoy, 2014).

In a 29-day study in which rats received a dietary concentration of fenpicoxamid of 0, 2300, 4500 or 9000 ppm (equal to 0, 196, 395 and 788 mg/kg bw per day for males and 0, 197, 377 and 764 mg/kg bw per day for females, respectively), the NOAEL was 9000 ppm (equal to 764 mg/kg bw per day), the highest dose tested (Stebbins, Murray & McCoy, 2012).

In a 90-day study in which rats received a dietary concentration of fenpicoxamid of 0, 3000, 6000 or 11 500/14 000 ppm (dose increased at day 71; equal to 0, 180, 365 and 732 mg/kg bw per day for males and 0, 205, 413 and 834 mg/kg bw per day for females, respectively), the NOAEL was 11 500/14 000 ppm (equal to 732 mg/kg bw per day), the highest dose tested (Stebbins et al., 2012).

In a 90-day study in which dogs received a dietary concentration of fenpicoxamid of 0, 3000, 10 000 or 30 000 ppm (equal to 0, 100, 408 and 939 mg/kg bw per day for males and 0, 122, 353 and 1115 mg/kg bw per day for females, respectively), the NOAEL was 30 000 ppm (equal to 939 mg/kg bw per day), the highest dose tested (Heward, 2013b).

In a 1-year study in which dogs received a dietary concentration of fenpicoxamid of 0, 3000, 10 000 or 30 000 ppm (equal to 0, 84, 300 and 981 mg/kg bw per day for males and 0, 80, 273 and 1011 mg/kg bw per day for females, respectively), the NOAEL was 3000 ppm (equal to 80 mg/kg bw per day), based on an increased incidence of thin appearance and increased total bilirubin in males and females and decreased body weight and increased liver changes in males at 10 000 ppm (equal to 273 mg/kg bw per day) (Heward, 2014).

In an 18-month carcinogenicity study in which mice received a dietary concentration of fenpicoxamid of 0, 50, 300 or 1500 ppm (males) or 0, 50, 300 or 3000 ppm (females) (equal to 0, 5.3, 32 and 156 mg/kg bw per day for males and 0, 6.8, 40 and 388 mg/kg bw per day for females, respectively), the NOAEL for toxicity was 50 ppm (equal to 5.3 mg/kg bw per day), based on altered liver metabolism and increased hepatocellular hypertrophy in males at 300 ppm (equal to 32 mg/kg bw per day). The NOAEL for carcinogenicity was 50 ppm (equal to 5.3 mg/kg bw per day), based on an equivocal increase in the incidence of liver adenomas in males at 300 ppm (equal to 32 mg/kg bw per day) (Thomas, Murray & McCoy, 2013).

In a 2-year toxicity and carcinogenicity study in which rats received a dietary concentration of fenpicoxamid of 0, 3000, 10 000 or 30 000 ppm adjusted to achieve intakes of 0, 101, 302 and 1009 mg/kg bw per day, a NOAEL for toxicity could not be identified, as increased thyroid weight, histopathological changes in the thyroid and increased blood iodide were observed at 101 mg/kg bw per day, the lowest dose tested. The NOAEL for carcinogenicity was 302 mg/kg bw per day, based on an increased incidence of ovarian adenocarcinomas at 1009 mg/kg bw per day (Stebbins et al., 2014).

The Meeting concluded that fenpicoxamid is carcinogenic in male mice and female rats, but not in female mice or male rats.

Fenpicoxamid was tested for genotoxicity in an adequate range of in vitro and in vivo assays. It was not mutagenic in bacterial or mammalian cells in vitro (Dakoulas & Divi, 2010; Schisler,

2011b,c). It caused chromosomal aberrations in rat lymphocytes in vitro (Schisler, 2011a), but it gave negative results in vivo in a mouse micronucleus test and unscheduled DNA synthesis assay (Schisler, 2011c; Pant, 2014).

The Meeting concluded that fenpicoxamid is unlikely to be genotoxic in vivo.

As fenpicoxamid is unlikely to be genotoxic in vivo and there is a clear threshold for liver adenomas in male mice and ovarian adenocarcinomas in female rats, the Meeting concluded that fenpicoxamid is unlikely to pose a carcinogenic risk to humans from the diet.

In a two-generation reproductive toxicity study in which rats received a dietary concentration of fenpicoxamid of 0, 1729, 5052 or 16 614 ppm in males and 0, 1362, 4005 or 13 383 ppm in females adjusted to provide achieved intakes of, respectively, 0, 107, 322 and 1066 mg/kg bw per day for males and 0, 105, 315 and 1052 mg/kg bw per day for females, the NOAEL for parental toxicity, reproductive toxicity and offspring toxicity was 1052 mg/kg bw per day, the highest dose tested (Ellis-Hutchings et al., 2013).

In a developmental toxicity study in which female rats received fenpicoxamid in the diet at a concentration of 0, 1350, 4050 or 13 500 ppm (equal to 0, 103, 311 and 1036 mg/kg bw per day, respectively) from GD 6 to GD 21, the NOAEL for maternal and embryo/fetal toxicity was 13 500 ppm (equal to 1036 mg/kg bw per day), the highest dose tested (Rasoulpour et al., 2012b).

In a developmental toxicity study in which female rabbits received fenpicoxamid in the diet at a concentration of 0, 1500, 5000 or 15 000 ppm (equal to 0, 52.8, 177 and 495 mg/kg bw per day, respectively) from GD 7 to GD 28, the NOAEL for maternal toxicity was 1500 ppm (equal to 52.8 mg/kg bw per day), based on decreased body weight gain, feed consumption and faecal output at 5000 ppm (equal to 177 mg/kg bw per day). The NOAEL for embryo and fetal toxicity was 15 000 ppm (equal to 495 mg/kg bw per day), the highest dose tested (Ellis-Hutchings, Bell & McCoy, 2013).

No neurotoxicity or immunotoxicity studies were available, but there was no indication of neurotoxic or immunotoxic effects in the short- or long-term toxicity studies.

No information on the potential effects of fenpicoxamid on the microbiome of the human gastrointestinal tract is available.

Toxicological data on metabolites and/or degradates

The acute oral LD_{50} of X642188, a rat and crop metabolite, was greater than 2000 mg/kg bw (Dalal, 2013). X642188 was negative in the Ames test (Patel, 2012). For chronic toxicity, the threshold of toxicological concern (TTC) approach (Cramer class III) could be applied.

No toxicity information was available for any other metabolites and/or degradates. However, based on structure–activity considerations, the TTC approach (Cramer class III) could be applied to X12264475 (animal metabolite and processing product), X12314005 (crop metabolite and processing product) and X12335723 (processing product) for the assessment of chronic toxicity.

Insufficient information was available to evaluate the toxicological relevance of the metabolites X12326349 (animal metabolite), X696872 (animal metabolite) and X12019520 (simulated processing product).

Human data

In reports on manufacturing plant personnel, no adverse health effects were noted (Dow, 2016).

The Meeting concluded that the existing database on fenpicoxamid was adequate to characterize the potential hazards to the general population, including fetuses, infants and children.

Toxicological evaluation

The Meeting established an acceptable daily intake (ADI) of 0–0.05 mg/kg bw, on the basis of the NOAEL of 5.3 mg/kg bw per day from the 18-month mouse carcinogenicity study for liver changes and an equivocal increase in the incidence of liver adenomas at 32 mg/kg bw per day in males. A safety factor of 100 was applied. The Meeting noted that there was a margin of 600 between the upper bound of the ADI and the LOAEL for adenomas in mice and a margin of 2000 relative to the LOAEL (the lowest dose tested) for non-neoplastic effects on the thyroid in the 2-year study in rats.

The Meeting concluded that it was not necessary to establish an acute reference dose (ARfD) for fenpicoxamid in view of its low acute oral toxicity and the absence of any other toxicological effects, including developmental toxicity, that would be likely to be elicited by a single dose.

Levels relevant to risk assessment of fenpicoxamid

Species	Study	Effect	NOAEL	LOAEL
Mouse	Eighteen-month study of carcinogenicity[a]	Toxicity	50 ppm, equal to 5.3 mg/kg bw per day	300 ppm, equal to 32 mg/kg bw per day
		Carcinogenicity	50 ppm, equal to 5.3 mg/kg bw per day	300 ppm, equal to 32 mg/kg bw per day
Rat	Two-year study of toxicity and carcinogenicity[a]	Toxicity	–	101 mg/kg bw per day[b]
		Carcinogenicity	302 mg/kg bw per day	1 009 mg/kg bw per day
	Two-generation study of reproductive toxicity[a]	Reproductive toxicity	1 052 mg/kg bw per day[c]	–
		Parental toxicity	1 052 mg/kg bw per day[c]	–
		Offspring toxicity	1 052 mg/kg bw per day[c]	_
	Developmental toxicity study[a]	Maternal toxicity	13 500 ppm, equal to 1 036 mg/kg bw per day[c]	_
		Embryo and fetal toxicity	13 500 ppm, equal to 1 036 mg/kg bw per day[c]	_
Rabbit	Developmental toxicity study[a]	Maternal toxicity	1 500 ppm, equal to 52.8 mg/kg bw per day	5 000 ppm, equal to 177 mg/kg bw per day
		Embryo and fetal toxicity	15 000 ppm, equal to 495 mg/kg bw per day[c]	_
Dog	One-year study of toxicity[a]	Toxicity	3 000 ppm, equal to 80 mg/kg bw per day	10 000 ppm, equal to 273 mg/kg bw per day

[a] Dietary administration.
[b] Lowest dose tested.
[c] Highest dose tested.

Acceptable daily intake (ADI)

0–0.05 mg/kg bw

Acute reference dose (ARfD)

Unnecessary

Information that would be useful for the continued evaluation of the compound

Results from epidemiological, occupational health and other such observational studies of human exposure

Critical end-points for setting guidance values for exposure to fenpicoxamid

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid, but low
Dermal absorption	No data
Distribution	Wide; higher concentrations in plasma, liver, kidney and urinary bladder
Potential for accumulation	No evidence of accumulation
Rate and extent of excretion	Rapid and complete; primarily via the faeces; 58–90% eliminated within 24 hours
Metabolism in animals	Large percentage not absorbed and bound within faeces; otherwise extensively metabolized
Toxicologically significant compounds in animals and plants	Fenpicoxamid
Acute toxicity	
Rat, LD_{50}, oral	>2 000 mg/kg bw
Rat, LD_{50}, dermal	>5 000 mg/kg bw
Rat, LC_{50}, inhalation	>0.53 mg/L
Rabbit, dermal irritation	Non-irritating
Rabbit, ocular irritation	Minimally irritating
Mouse, dermal sensitization	Not sensitizing
Short-term studies of toxicity	
Target/critical effect	Thin appearance, decreased body weight and liver changes
Lowest relevant oral NOAEL	80 mg/kg bw per day (dog)
Lowest relevant dermal NOAEL	No data
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Liver changes and adenomas
Lowest relevant NOAEL	5.3 mg/kg bw per day (male mouse)

Carcinogenicity	Carcinogenic in male mice and female rats; not carcinogenic in female mice or male rats[a]
Genotoxicity	
	No evidence of genotoxicity in vivo[a]
Reproductive toxicity	
Target/critical effect	None
Lowest relevant parental NOAEL	1 052 mg/kg bw per day, highest dose tested (rat)
Lowest relevant offspring NOAEL	1 052 mg/kg bw per day, highest dose tested (rat)
Lowest relevant reproductive NOAEL	1 052 mg/kg bw per day, highest dose tested (rat)
Developmental toxicity	
Target/critical effect	Decreased feed consumption, body weight gain and faecal output
Lowest relevant maternal NOAEL	52.8 mg/kg bw per day (rabbit)
Lowest relevant embryo/fetal NOAEL	495 mg/kg bw per day, highest dose tested (rabbit)
Neurotoxicity	
Acute neurotoxicity NOAEL	No data
Subchronic neurotoxicity NOAEL	No data
Developmental neurotoxicity NOAEL	No data
Other toxicological studies	
Immunotoxicity	No data
Studies on toxicologically relevant metabolites	
X642188	LD_{50} > 2 000 mg/kg bw No evidence of genotoxicity
Human data	
	No adverse health effects noted in manufacturing plant personnel

[a] Unlikely to pose a carcinogenic risk to humans via exposure from the diet.

Summary

	Value	Study	Safety factor
ADI	0–0.05 mg/kg bw	Eighteen-month carcinogenicity study in mice	100
ARfD	Unnecessary	–	–

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